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I, KIM MARSHALL, MANAGER EXAMINATION SUPPORT AND SALES, hereby certify that the annexed is a true copy of the Provisional specification in connection with Application No. PO 7359 for a patent by FUJISAWA PHARMACEUTICAL Co., LTD filed on 17 June 1997.

I further certify that the annexed specification is not, as yet, open to public inspection.

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WITNESS my hand this Sixteenth day of June 1998

KIM MARSHALL
MANAGER EXAMINATION SUPPORT AND SALES

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Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION
for the invention entitled:

"Piperazine derivatives"

The invention is described in the following statement:

PIPERAZINE DERIVATIVES

The present invention relates to new piperazine derivatives and a salt thereof.

More particularly, it relates to new piperazine derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

Accordingly, one object of the present invention is to provide new and useful piperazine derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like.

Another object of the present invention is to provide a process for the preparation of said piperazine derivatives and a salt thereof.

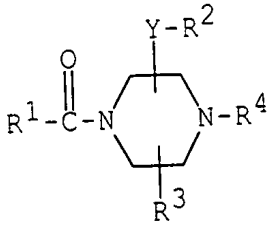
A further object of the present invention is to provide

a pharmaceutical composition comprising, as an active ingredient, said piperazine derivatives and a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said piperazine derivatives or a pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g., migraine, headache, toothache, cancerous pain, back pain, etc.); and the like in human being or animals.

Some piperazine derivatives having pharmaceutical activities such as Tachykinin antagonism have been known as described in EP 0655442 A1.

The object compound of the present invention can be represented by the following general formula (I) :



(I)

wherein

Y is bond or lower alkylene,

R^1 is aryl which may have substituent(s),

R^2 is aryl or indolyl, each of which may have substituent(s),

R^3 is hydrogen or lower alkyl,

R^4 is pyridyl(lower)alkylamino(lower)alkynyl;

N-(lower alkyl)-N-[pyridyl(lower)alkyl]amino(lower)-alkyl;

hydroxy(lower)alkoxy(lower)alkyl;

lower alkanoyl(lower)alkoxy(lower)alkyl;

phenyl(lower)alkyl which may have lower alkoxycarbonyl, carboxy, hydroxy(lower)alkyl or morpholinyl(lower)alkyl;

(2-pyridyl)(lower)alkyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl and halogen;

(3-pyridyl)propyl which may have lower alkoxy;

(3-pyridyl)butyl;

(3-pyridyl)(lower)alkenyl;

(2-pyridyl)(lower)alkynyl;

(3-pyridyl)(lower)alkynyl which may have lower alkoxy or amino;

pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have substituent(s);

imidazolyl(lower)alkyl which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

pyrazolyl(lower)alkyl which may have hydroxy(lower)alkyl, carboxy(lower)alkyl, lower alkoxycarbonyl(lower)alkyl, morpholinyl(lower)alkyl or morpholinylcarbonyl(lower)alkyl;

thiazolyl(lower)alkyl which may have lower alkyl; or

saturated heterocyclic(lower)alkyl,

saturated heterocyclic(lower)alkenyl,
saturated heterocyclic(lower)alkynyl,
saturated heterocyclicamino(lower)alkyl,
saturated heterocyclicimino(lower)alkyl,
saturated heterocyclicaminocarbonyl(lower)alkyl or
saturated heterocyclic(lower)alkoxy(lower)alkyl, each of which may have substituent(s).

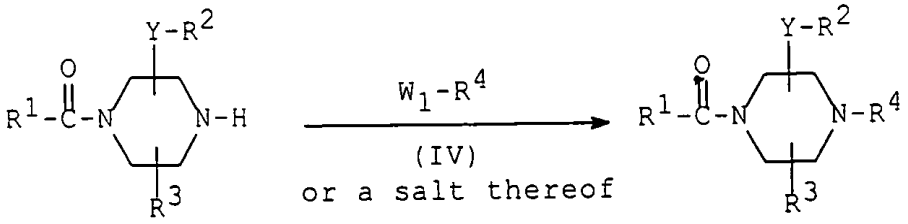
It is to be noted that the object compound (I) may include one or more stereoisomers due to asymmetric carbon atom(s) and double bond, and all of such isomers and a mixture thereof are included within the scope of the present invention.

It is further to be noted that isomerization or rearrangement of the object compound (I) may occur due to the effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

According to the present invention, the object compound (I) or a salt thereof can be prepared by processes which are illustrated in the following schemes.

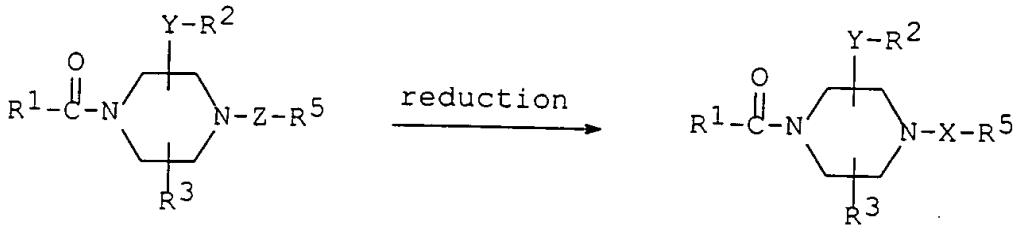
Process 1



(II)
or its reactive derivative at the imino group or a salt thereof

(I)
or a salt thereof

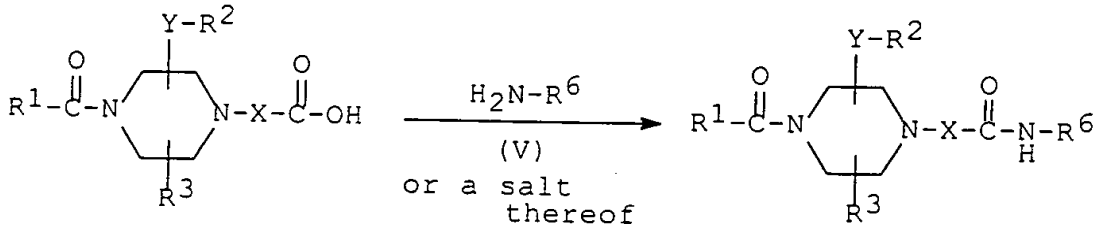
Process 2



(Ia)
or a salt thereof

(Ib)
or a salt thereof

Process 3

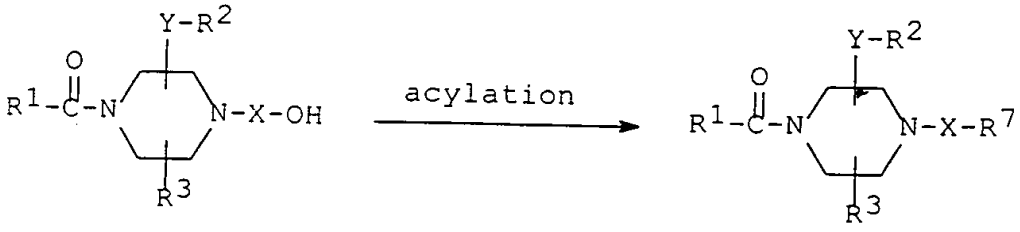


(III)
or its reactive derivative at the carboxy group
or a salt thereof

(V)
or a salt thereof

(Ic)
or a salt thereof

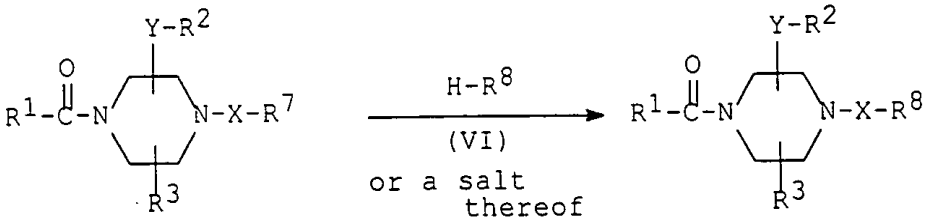
Process 4



(Id)
or a salt thereof

(Ie)
or a salt thereof

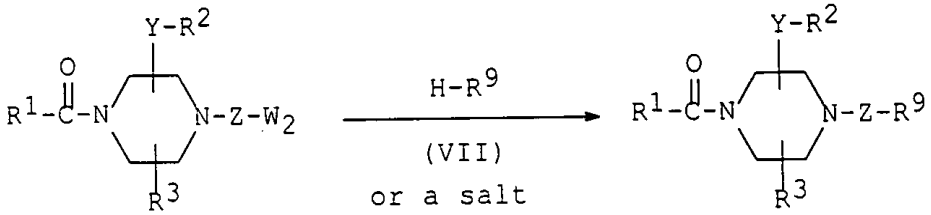
Process 5



(Ie)
or a salt thereof

(If)
or a salt thereof

Process 6



(Ig)
or a salt thereof

(Ih)
or a salt thereof

wherein
Y, R^1, R^2, R^3 and R^4 are each as defined above,
X is lower alkylene,
Z is lower alkynylene,
R^5 is pyridyl(lower)alkylamino, 2-pyridyl, 3-pyridyl or saturated heterocyclic which may have substituent(s),
R^6 is saturated heterocyclic which may have substituent(s),
R^7 is acyloxy,
R^8 is N-(lower alkyl)-N-[pyridyl(lower)alkyl]amino; imidazolyl which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen; pyrazolyl which may have hydroxy(lower)alkyl, carboxy(lower)alkyl, lower alkoxycarbonyl(lower)alkyl, morpholinyl(lower)alkyl or

morpholinylcarbonyl(lower)alkyl; thiazolyl which may have lower alkyl; or

saturated heterocyclic which may have substituent(s),

R^9 is pyridyl(lower)alkylamino or saturated heterocyclic which may have substituent(s), and

W_1 and W_2 are each a leaving group.

As to the starting compounds (II), (III), (IV), (V), (VI) and (VII), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or similar manners thereto.

Suitable salts of the starting and object compounds are conventional non-toxic and pharmaceutically acceptable salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, propylene, tetramethylene, methylmethylene, methyltrimethylene, hexamethylene, and the like, in which the preferred one is methylene, ethylene, trimethylene or methylmethylene.

Suitable "lower alkynylene" may include one having 2 to 6 carbon atoms, such as ethynylene, propynylene, butynylene, and the like, in which the preferred one is propynylene or butynylene.

Suitable "halogen" and "halogen" moiety in the terms "mono(or di or tri)halo(lower)alkyl", "mono(or di or tri)halo(C_1-C_4)alkyl", etc. may include fluorine, chlorine, bromine and iodine.

Suitable "lower alkyl" and "lower alkyl" moiety in the terms "pyridyl(lower)alkylamino(lower)alkynyl", "N-(lower alkyl)-N-[pyridyl(lower)alkyl]amino(lower)alkyl", etc. may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl and the like, preferably one having 1 to 5 carbon atom(s).

Suitable "lower alkenyl" moiety in the terms "3-pyridyl(lower)alkenyl", "saturated heterocyclic(lower)alkenyl", etc. may include vinyl, 1-(or 2-)propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)hexenyl, methylvinyl, ethylvinyl, 1-(or 2- or 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or 2-)propenyl, 1-(or 2- or 3- or 4-)methyl-1-(or 2- or 3-)butenyl, and the like, in which more preferable example may be C_2-C_4 alkenyl.

Suitable "lower alkynyl" moiety in the terms "pyridyl(lower)alkylamino(lower)alkynyl", "(2-pyridyl)-(lower)alkynyl", etc. may include ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1-(or 2- or 3-)-butynyl, 1-(or 3-)methyl-2-butynyl, 1-(or 3-)ethyl-2-butynyl,

1-(or 3-)propyl-2-butynyl, 1-(or 3-)isopropyl-2-butynyl, 1-(or 2- or 3- or 4-)pentynyl, 1-(or 2- or 3- or 4- or 5-)-hexynyl and the like, in which more preferable example may be C_2-C_5 alkynyl.

Suitable "aryl" may include phenyl, naphthyl, and the like, in which the preferred one is C_6-C_{10} aryl and the most preferred one is phenyl or naphthyl.

Suitable "lower alkanoyl" and "lower alkanoyl" moiety in the term "lower alkanoyl(lower)alkoxy(lower)alkyl" may include formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl and the like.

Suitable "lower alkoxy" and "lower alkoxy" moiety in the terms "hydroxy(lower)alkoxy(lower)alkyl", "lower alkanoyl(lower)alkoxy(lower)alkyl", etc. may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

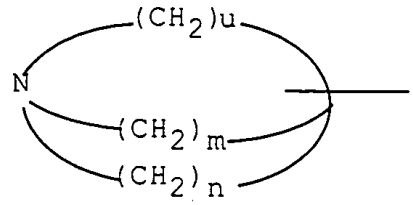
Suitable "saturated heterocyclic" and "saturated heterocyclic" moiety in the terms "saturated heterocyclic-(lower)alkyl", "saturated heterocyclic(lower)alkenyl", etc. may include

saturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, hexamethyleneimino, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, homomorpholinyl, sydnonyl, etc.;

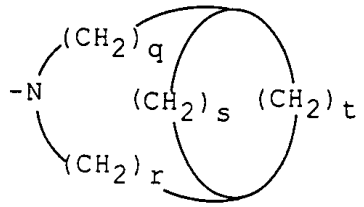
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, thiomorpholinyl, etc.;

saturated heterobicyclic group of the formula :



(wherein u, m and n are each integer of 1 to 6);

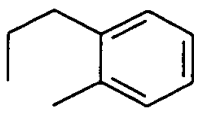
saturated heterobicyclic group of the formula :



(wherein q, r, s and t are each integer of 1 to 6); and the like.

Suitable "substituent" in the terms "aryl which may have substituent(s)", "aryl or indolyl, each of which may have substituent(s)", "pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have substituent(s)", "saturated heterocyclic(lower)alkyl, saturated heterocyclic-(lower)alkenyl, saturated heterocyclic(lower)alkynyl, saturated heterocyclicamino(lower)alkyl, saturated heterocyclicimino(lower)alkyl, saturated heterocyclicaminocarbonyl(lower)alkyl or saturated heterocyclic(lower)alkoxy(lower)alkyl, each of which may have substituent(s)" and "saturated heterocyclic which may have substituent(s)" may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.), cyclo(lower)alkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, etc.), lower alkoxy(lower)alkyl (e.g., methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-ethoxyethyl, 2-ethoxyethyl, etc.), lower

alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, etc.), lower alkenyl (e.g., vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl, etc.), lower alkynyl (e.g., ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or 5-hexynyl, etc.), mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.), halogen (e.g., chlorine, bromine, fluorine and iodine), carboxy, protected carboxy, hydroxy, protected hydroxy, aryl (e.g., phenyl, naphthyl, etc.), ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.), carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above, protected carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above, nitro, amino, protected amino, di(lower)alkylamino (e.g., dimethylamino, diethylamino, diisopropylamino, ethylmethylamino, isopropylmethylamino, ethylisopropylamino, etc.), hydroxy(lower)alkyl (e.g. hydroxymethyl, hydroxyethyl, etc.), protected hydroxy(lower)alkyl, acyl, cyano, oxo, mercapto, lower alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), lower alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, etc.), imino, morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, morpholino), bivalent group of the formula :



,

carboxy(lower)alkyl (e.g., carboxymethyl, carboxyethyl, carboxypropyl, etc.), lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, neopentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, etc.), spirocyclo(lower)alkyl (e.g., spirocyclopropyl, spirocyclobutyl, spirocyclopentyl, etc.), ar(lower)alkoxycarbonyl(lower)alkyl (e.g., benzyloxycarbonylmethyl, benzyloxycarbonylethyl, benzyloxycarbonylpropyl, etc.), pyridyl(lower)alkyl (e.g., pyridylmethyl, pyridylethyl, etc.), carbamoyl, lower alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di(lower alkyl)carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, etc.), and the like.

Suitable "leaving group" may include lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, etc.), aryloxy (e.g. phenoxy, naphthoxy, etc.), an acid residue or the like.

Suitable "acid residue" may be halogen (e.g. chlorine, bromine, iodine, etc.), sulfonyloxy (e.g. methylsulfonyloxy, phenylsulfonyloxy, mesitylenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

Suitable "acyloxy" may include hydroxysulfonyloxy, lower alkylsulfonyloxy (e.g. methylsulfonyloxy, ethylsulfonyloxy, etc.), phosphonooxy, and the like.

Preferred embodiments of the object compound (I) are as follows :

Y is lower alkylene (more preferably C_1-C_4 alkylene, most preferably methylene);

R^1 is aryl (more preferably C_6-C_{10} aryl, most preferably phenyl) which may have 1 to 3 (more preferably 1 or 2,

most preferably 2) substituent(s) [more preferably mono(or di or tri)halo(lower)alkyl (more preferably trihalo(lower)alkyl, most preferably trifluoromethyl) or halogen (more preferably chlorine)];

R^2 is aryl (more preferably C_6-C_{10} aryl, most preferably phenyl or naphthyl) or indolyl, each of which may have 1 to 3 (more preferably 1 or 2) substituent(s) [more preferably substituent selected from the group consisting of lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl) and mono(or di or tri)halo(lower)alkyl (more preferably mono(or di or tri)halo(C_1-C_4)alkyl, most preferably trifluoromethyl)];

R^3 is hydrogen; and

R^4 is pyridyl(lower)alkylamino(lower)alkynyl (more preferably pyridyl(C_1-C_4)alkylamino(C_2-C_4)alkynyl, most preferably 4-[(3-pyridylmethyl)amino]-2-butynyl);

N-(lower alkyl)-N-[pyridyl(lower)alkyl]amino(lower)alkyl [more preferably N-(C_1-C_4 alkyl)-N-[pyridyl(C_1-C_4)-alkyl]amino(C_1-C_4)alkyl, more preferably 2-[N-methyl-N-(3-pyridylmethyl)amino]ethyl];

hydroxy(lower)alkoxy(lower)alkyl (more preferably hydroxy(C_1-C_4)alkoxy(C_1-C_4)alkyl, most preferably (hydroxyethoxy)ethyl);

lower alkanoyl(lower)alkoxy(lower)alkyl (more preferably C_1-C_4 alkanoyl(C_1-C_4)alkoxy(C_1-C_4)alkyl, most preferably formylmethoxyethyl);

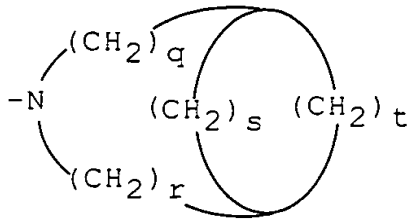
phenyl(lower)alkyl (more preferably phenyl(C_1-C_4)alkyl, most preferably benzyl) which may have lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably methoxycarbonyl), carboxy, hydroxy(lower)alkyl (more preferably hydorxy(C_1-C_4)-alkyl, most preferably hydroxymethyl) or morpholinyl(lower)alkyl (more preferably morpholinyl-(C_1-C_4)alkyl, most preferably morpholinomethyl [more preferably α-(methoxycarbonyl)benzyl, α-carboxybenzyl,

α-(hydroxymethyl)benzyl or α-(morpholinomethyl)benzyl];
(2-pyridyl)(lower)alkyl (more preferably (2-pyridyl)-(C_1-C_4)alkyl, more preferably (2-pyridyl)propyl or (2-pyridyl)butyl which may have 1 to 3 (more preferably 1 or 2) substituent(s) selected from the group consisting of lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl), lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy), mono(or di or tri)halo(lower)alkyl (more preferably trihalo(C_1-C_4)alkyl, most preferably trifluoromethyl) and halogen (more preferably fluorine));
(3-pyridyl)propyl (more preferably 3-(3-pyridyl)propyl) which may have lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy);
(3-pyridyl)butyl (more preferably 4-(3-pyridyl)butyl);
(3-pyridyl)(lower)alkenyl (more preferably (3-pyridyl)(C_2-C_4)alkenyl, most preferably 3-(3-pyridyl)-2-propenyl);
(2-pyridyl)(lower)alkynyl (more preferably (2-pyridyl)(C_2-C_4)alkynyl, most preferably 3-(2-pyridyl)-2-propynyl or 4-(2-pyridyl)-3-butynyl);
(3-pyridyl)(lower)alkynyl (more preferably (3-pyridyl)(C_2-C_4)alkynyl, most preferably 3-(3-pyridyl)-2-propynyl or 4-(3-pyridyl)-3-butynyl) which may have lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy) or amino;
pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have 1 to 3 (more preferably 1 or 2) substituent(s) [more preferably substituent selected from the group consisting of lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl or isopropyl), ar(lower)alkyl (more preferably phenyl(C_1-C_4)alkyl, most preferably benzyl) and pyridyl(lower)alkyl (more preferably pyridyl(C_1-C_4)alkyl, most preferably pyridylmethyl)];

imidazolyl(lower)alkyl (more preferably imidazolyl-(C_1-C_4)alkyl, most preferably 3-(1H-imidazol-1-yl)propyl) which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl or isopropyl), lower alkynyl (more preferably C_2-C_5 alkynyl, most preferably propargyl), ar(lower)alkyl (more preferably phenyl(C_1-C_4)alkyl, most preferably benzyl), pyridyl(lower)alkyl (more preferably pyridyl(C_1-C_4)alkyl most preferably pyridylmethyl), mono(or di or tri)halo(lower)alkyl (more preferably trihalo(C_1-C_4)alkyl, most preferably trifluoromethyl) and halogen (more preferably fluorine);
pyrazolyl(lower)alkyl (more preferably pyrazolyl(C_1-C_4)-alkyl, most preferably (1H-pyrazol-4-yl)methyl or 3-(1H-pyrazol-1-yl)propyl) which may have hydroxy(lower)alkyl (more preferably hydroxy(C_1-C_4)alkyl, most preferably 2-hydroxyethyl), carboxy(lower)alkyl (more preferably carboxy(C_1-C_4)alkyl, most preferably carboxymethyl), lower alkoxycarbonyl(lower)alkyl (more preferably C_1-C_4 alkoxycarbonyl(C_1-C_4)alkyl, most preferably tert-butoxycarbonylmethyl), morpholinyl(lower)alkyl (more preferably morpholinyl(C_1-C_4)alkyl, most preferably 2-morpholinoethyl) or morpholinylcarbonyl(lower)alkyl (more preferably morpholinylcarbonyl(C_1-C_4)alkyl, most preferably morpholinocarbonylmethyl);
thiazolyl(lower)alkyl (more preferably thiazoly(C_1-C_4)-alkyl, most preferably 4-thiazolymethyl) which may have lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl); or
saturated heterocyclic(lower)alkyl (more preferably saturated heterocyclic(C_1-C_4)alkyl, most preferably saturated heterocyclicethyl or saturated heterocyclicpropyl),
saturated heterocyclic(lower)alkenyl (more preferably

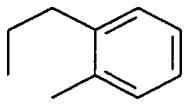
saturated heterocyclic(C_2-C_4)alkenyl, most preferably saturated heterocyclicpropenyl or saturated heterocyclicbutenyl), saturated heterocyclic(lower)alkynyl (more preferably saturated heterocyclic(C_2-C_5)alkynyl, most preferably saturated heterocyclicbutynyl or saturated heterocyclicpentynyl), saturated heterocyclicamino(lower)alkyl (more preferably saturated heterocyclicamino(C_1-C_4)alkyl, most preferably saturated heterocyclicaminopropyl), saturated heterocyclicimino(lower)alkyl (more preferably saturated heterocyclicimino(C_1-C_4)alkyl, most preferably saturated heterocycliciminoethyl), saturated heterocyclicaminocarbonyl(lower)alkyl (more preferably saturated heterocyclicaminocarbonyl(C_1-C_4)-alkyl, most preferably saturated heterocyclicaminocarbonylmethyl) or saturated heterocyclic(lower)alkoxy(lower)alkyl (more preferably saturated heterocyclic(C_1-C_4)alkoxy(C_1-C_4)alkyl, most preferably saturated heterocyclicethoxyethyl) [wherein "saturated heterocyclic" moiety is saturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 (more preferably 1 or 2) nitrogen atom(s) (more preferably pyrrolidinyl, piperidyl or piperazinyl);
saturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 or 2 (more preferably 1) oxygen atom(s) and 1 to 3 (more preferably 1) nitrogen atom(s) (more preferably morpholinyl or homomorpholinyl);
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 (more preferably 1) sulfur atom(s) and 1 to 3 (more preferably 1) nitrogen atom(s) (more preferably thiomorpholinyl);
or

saturated heterocyclic group of the formula :



(wherein q, r, s and t are each as defined above)

(more preferably 3-azabicyclo[3.2.2]non-3-yl)], each of which may have 1 to 3 (more preferably 1 or 2) suitable substituent(s) [more preferably substituent selected from the group consisting of cyclo(lower)alkyl (more preferably cyclohexyl), lower alkanoyl (more preferably C_1-C_4 alkanoyl, most preferably formyl), lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl, ethyl, isopropyl or isobutyl), mono(or di or tri)halo(lower)alkyl (more preferably monohalo(C_1-C_4)-alkyl or trihalo(C_1-C_4)alkyl, most preferably fluoromethyl or trifluoromethyl), lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy), lower alkoxy(lower)alkyl (more preferably C_1-C_4 alkoxy(C_1-C_4)-alkyl, most preferably methoxymethyl), halogen (more preferably chlorine or fluorine), aryl (more preferably phenyl), cyano, oxo, bivalent group of the formula :



carboxy(lower)alkyl (more preferably carboxy(C_1-C_4)-alkyl, most preferably carboxypropyl), lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably tert-butoxycarbonyl), spirocyclo(lower)alkyl (more preferably spirocyclo-(C_1-C_4)alkyl, most preferably spirocyclopropyl), ar(lower)alkoxycarbonyl(lower)alkyl (more preferably

benzyloxycarbonyl(C_1-C_4)alkyl, most preferably benzyloxycarbonylpropyl), hydroxy(lower)alkyl (more preferably hydroxy(C_1-C_4)alkyl, most preferably hydroxymethyl), carbamoyl, lower alkylcarbamoyl (more preferably C_1-C_4 alkylcarbamoyl, most preferably methylcarbamoyl) and di(lower alkyl)carbamoyl (more preferably di(C_1-C_4 alkyl)carbamoyl, most preferably dimethylcarbamoyl)].

More preferred embodiments of the object compound (I) are as follows :

Y is lower alkylene (more preferably C_1-C_4 alkylene, most preferably methylene);

R^1 is phenyl which may have 1 or 2 mono(or di or tri)halo-(lower)alkyl or halogen (more preferably chlorine) [more preferably bis(trihalo(lower)alkyl)phenyl or dichlorophenyl, most preferably bis(trifluoromethyl)phenyl];

R^2 is phenyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of lower alkyl and mono(or di or tri)halo(lower)alkyl [more preferably di(lower alkyl)phenyl or [trihalo(lower)alkyl]phenyl, most preferably dimethylphenyl or (trifluoromethyl)phenyl], naphthyl or indolyl;

R^3 is hydrogen; and

R^4 is pyridyl(lower)alkylamino(lower)alkynyl (more preferably pyridyl(C_1-C_4)alkylamino(C_2-C_4)alkynyl, most preferably 4-[(3-pyridylmethyl)amino]-2-butynyl) or (2-pyridyl)(lower)alkyl (more preferably (2-pyridyl)-(C_1-C_4)alkyl, more preferably (2-pyridyl)propyl or (2-pyridyl)butyl, most preferably 3-(2-pyridyl)propyl.

Another more preferred embodiments of the object compound I are as follows :

Y is lower alkylene,

R^1 is C_6-C_{10} aryl which may have 1 or 2 mono(or di or tri)halo(lower)alkyl,

R^2 is C_6-C_{10} aryl or indolyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl and halogen,

R^3 is hydrogen, and

R^4 is pyridyl(lower)alkylamino(lower)alkynyl;

(2-pyridyl)propyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl and halogen;

pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl, ar(lower)alkyl and pyridyl(lower)alkyl;

imidazolyl(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

(2-methyl-1H-imidazol-4-yl)(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of isopropyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

(5-methyl-1H-imidazol-4-yl)(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of isopropyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

(3-morpholinyl)(lower)alkenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and aryl;

(3-morpholinyl)(lower)alkynyl which may have 1 to 3

substituent(s) selected from the group consisting of lower alkyl and aryl;
morpholino(lower)alkynyl which have a subsitutuent selected from the group consisting of carbamoyl, lower alkylcarbamoyl, di(lower alkyl)carbamoyl, hydroxy(lower)alkyl and aryl;
[3-[mono(or di or tri)halo(lower)alkyl]morpholino]-(lower)alkynyl;
morpholino(lower)alkenyl which have aryl; or
morpholino(lower)alkynyl which have 1 or 2 subsitutuent(s) selected from the group consisting of lower alkyl, aryl and halogen at the 2nd position of the morpholino group.

The Processes 1 to 6 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the imino group or a salt thereof with the compound (IV) or a salt thereof.

Suitable reactive derivative at the imino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol,

etc.], acetone, dioxene, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

The reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 2

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to a reduction reaction.

The reaction can be carried out in the manner disclosed in Example 3 mentioned later or similar manners thereto.

Process 3

The object compound (Ic) or a salt thereof can be prepared by reacting the compound (III) or its reactive derivative at the carboxy group or a salt thereof with the compound (V) or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. The suitable example of the reactive derivative may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.],

dialkylphosphorous acid, lower alkanesulfonic acid [e.g. methanesulfonic acid, ethanesulfonic acid, etc.], sulfurous acid, thiosulfuric acid, sulfuric acid, aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, valeric acid, isovaleric acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromaticcarboxylic acid [e.g. benzoic acid, etc.]; a symmetrical and anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or a salt thereof, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dichlorohexylcarbodiimide;

N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thienyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)-isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; 2-chloro-1-methylpyridinium iodide; 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; so-called vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 4

The object compound (Ie) or a salt thereof can be prepared by subjecting the compound (Id) or a salt thereof to an acylation reaction.

The reaction can be carried out in the manner disclosed in Example 39 mentioned later or similar manners thereto.

Process 5

The object compound (If) or a salt thereof can be prepared by reacting the compound (Ie) or a salt thereof with the compound (VI) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, acetonitrile, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction may be also carried out in the presence of an inorganic or an organic base such as alkali metal (e.g., sodium, potassium, etc.), alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g. sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Process 6

The object compound (Ih) or a salt thereof can be prepared by reacting the compound (Ig) or a salt thereof with the compound (VII) or a salt thereof.

The reaction can be carried out in the manner disclosed in Example 30 mentioned later or similar manners thereto.

The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B antagonism, and therefore are useful for treating or preventing Tachykinin-mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma, bronchitis (e.g. chronic bronchitis, acute bronchitis and diffuse panbronchiolitis, etc.), rhinitis, couph, expectoration, and the like;
ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like;
cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like;
pains or aches (e.g. migraine, headache, cluster headache, toothache, cancerous pain, back pain, neuralgia, etc.); and the like.

Further, it is expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like;
gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like;
inflammatory diseases such as nephritis, and the like;
circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, Raynaud's disease, and the like;
epilepsy; spastic paralysis; pollakiuria; cystitis; bladder detrusor hyperreflexia; urinary incontinence; Parkinson diseases; dementia; AIDS related dementia; Alzheimer's diseases; Down's syndrome; Huntington's chorea; carcinoid syndrome; disorders related to immune enhancement or suppression; disorders caused by Helicobacter pylori or another spiral urease-positive gram-negative bacterium;

sunburn; angiogenesis or diseases caused by angiogenesis; and the like.

It is furthermore expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing chronic obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; proliferative vitreoretinopathy; psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; tenalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis; mental diseases, particularly anxiety, depression, dysthymic disorders and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis; and the like.

Furthermore, the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are Central Nervous System (CNS) penetrant.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compound, as an active ingredient, in

admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external including topical, enternal, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration. The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating Tachykinin-mediated diseases such as asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to show the utility of the object compound (I) and a pharmaceutically acceptable salt thereof, the pharmacological test data of some representative compounds of the present invention is shown in the following.

A. Evaluation of NK_1 antagonist transport efficiency to the cental nervous system using a h-NK_1 receptor binding assay

[I] Test Method

(1) Administration of test compound and extraction of the compound from brain

Male SD rats were given an i.v. injection of a solution containing a test compound (1 mg/kg). 5 Min later the

animals were anesthetized by ether, bled and perfused through the aorta ascendens with 20 ml of saline. The brain was rapidly removed, weighed and homogenized in 4 vol. ice-cold distilled water by using Polytoron (KINEMATICA). To extract the test compound, 500 µl of the homogenate, 100 µl of methanol, 500 µl of 0.1 N NaOH and 4 ml of ethyl acetate were mixed by shaking for 10 min at room temperature. The organic phase (2.5 ml) was recovered by centrifugation at 3,000 rpm for 10 min, dried and dissolved in dimethyl sulfoxide.

(2) h-NK_1 receptor binding assay

(a) Crude CHO cell membrane preparation

CHO cells permanently expressing h-NK_1 receptors were harvested and homogenized with a Dounce homogenizer at 4°C in a buffer (0.25 M sucrose, 25 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 1 mM EDTA, 5 µg/ml p-APMSF). The homogenate was centrifuged (500 x g, 10 min), and the pellet was resuspended in the same buffer, homogenized, and centrifuged. The two supernatants were combined and centrifuged (100,000 x g, 1 hour). The crude cell membranes thus isolated were resuspended in a buffer (25 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 1 mM EDTA, 5 µg/ml p-APMSF) and stored at -80°C until use.

(b) ^{125}I-BH-Substance P binding to the prepared membrane

Cell membranes (6 µg/ml) were incubated with ^{125}I-BH-Substance P (0.1 nM) with or without the extracted compounds in 0.25 ml of a medium (50 mM Tris-HCl (pH 7.4), 5 mM $MnCl_2$, 20 µg/ml chymostatin, 40 µg/ml bacitracin, 4 µg/ml leupeptin, 5 µg/ml p-APMSF, 200 µg/ml BSA) at 22°C for 90 min. At the end of the incubation period, the contents were quickly filtered through a Blue Mat 11740 filter (pretreated with

0.1% polyethylenimine for 3 hours prior to use) by using SKATRON Cell Harvester. The filter was then washed with a washing buffer (50 mM Tris-HCl (pH 7.4), 5 mM $MnCl_2$). The radioactivity was counted by using an auto gamma counter (Packard RIASTAR 5420A). All data presented are specific binding defined as that displaceable by 3 μM unlabeled Substance P.

[II] Test Result

All of the following Test Compounds showed more than 80% inhibition rate of ^{125}I-BH-Substance P binding to h-NK_1 receptors at the dose of 1 mg/kg.

Test Compounds : The object compounds of the Examples 1-(1), 5-(2), 6-(1), 15, 16-(2), 17, 18, 22, 29, 30, 38, 40, 45 and 56-(2)

B. Emesis in the ferret

[I] Test Method

Individually housed adult male ferrets (Marshall Farms, 1.4 to 2.2 kg) were given an i.v. injection of a solution contatining a test compound. 30 Min later the emetic responses (retching and vomiting) were induced by administration of intra-gastric copper sulfate (40 mg/kg/ml) and observed for the next 30 min. The timing and number of retches and vomits observed were recorded for each animal. An individual animal was tested with at least 10 days between experiments.

[II] Test Result

All of the following Test Compounds showed 100% inhibition rate of emesis in the ferret at the dose of 1.0

mg/kg.

Test compounds : The object compounds of the Examples 4-(2), 26, 29, 40 and 41

5

(to be continued on the next page)

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

A mixture of 3-bromopyridine (6.25 ml), propargyl alcohol (4.9 ml), bis(triphenylphosphine)palladium(II) chloride (0.45 g) and copper iodide (125 mg) in triethylamine (100 ml) was stirred under reflux for 1.5 hours. After being cooled at room temperature, the reaction mixture was filtered and the insoluble material on the filter was washed with ethyl acetate (about 200 ml). The filtrate and the washing were combined and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate as eluent. The fractions containing the objective compound were collected and evaporated under reduced pressure to give 3-(3-pyridyl)-2-propyn-1-ol (7.9 g) as brownish crystals.

IR (Nujol) : 3160, 1480, 1460, 1400 cm^{-1}

NMR ($CDCl_3$, δ) : 3.87 (1H, t, J=5.9Hz), 4.51 (2H, d, J=5.9Hz), 7.24-7.30 (1H, m), 7.73 (1H, dd, J=1.9 and 7.4Hz), 8.52 (1H, d, J=5.1Hz), 8.78 (1H, d, J=1.9Hz)

MASS : 134 $(M+H)^+$

Preparation 2

The following compounds were obtained according to a similar manner to that of Preparation 1.

(1) 4-(3-Pyridyl)-3-butyn-1-ol

NMR ($CDCl_3$, δ) : 2.61 (1H, s), 2.71 (2H, t, J=6.3Hz), 3.85 (2H, t, J=6.3Hz), 7.19-7.25 (1H, m), 7.70 (1H, dd, J=2.0, 8.0Hz), 8.48 (1H, dd, J=1.4, 5.0Hz), 8.63 (1H, d, J=1.4Hz)

MASS : 279, 148 $(M+H)^+$

(2) 3-(6-Methoxypyridin-3-yl)-2-propyn-1-ol

IR (Nujol) : 3300, 1610, 1560, 1490, 1460, 1370, 1350, 1310, 1300 cm^{-1}

NMR ($CDCl_3$, δ) : 3.94 (3H, s), 4.52 (2H, s), 6.70 (1H, dd, J=0.7, 8.6Hz), 7.60 (1H, dd, J=2.2, 8.6Hz), 8.30 (1H, d, J=2.2Hz)

MASS : 164 $(M+H)^+$, 134

(3) 3-(4-Methoxypyridin-3-yl)-2-propyn-1-ol

IR (KBr) : 3172, 2854, 1585, 1498 cm^{-1}

NMR ($CDCl_3$, δ) : 3.90 (3H, s), 4.33 (2H, d, J=4.0Hz), 5.38 (1H, t, J=4.0Hz), 7.12 (1H, d, J=5.8Hz), 8.24 (2H, br s)

MASS : 164 $(M+H)^+$, 134

(4) 3-[6-(tert-Butoxycarbonylamino)pyridin-3-yl]-2-propyn-1-ol

IR (Nujol) : 3500, 3210, 1725, 1625, 1600, 1580, 1430, 1380 cm^{-1}

NMR ($CDCl_3$, δ) : 1.54 (9H, s), 4.99 (2H, s), 7.70 (1H, dd, J=2.2, 8.7Hz), 7.97 (1H, d, J=8.7Hz), 8.40 (1H, d, J=2.2Hz), 8.51 (1H, br s)

MASS : 217 $(M+H)^+$, 175

Preparation 3

Thionyl chloride (11.9 g) was added dropwise to a solution of 3-(3-pyridyl)-2-propyn-1-ol (13.3 g) in dichloromethane (266 ml) at room temperature. After completion of the addition, the mixture was stirred for 2 hours at room temperature. The resulting precipitates were collected by filtration and washed with diethyl ether to give 1-chloro-3-(3-pyridyl)-2-propyne hydrochloride (14.5 g) as brownish crystals.

Preparation 4

The following compounds were obtained according to a similar manner to that of Preparation 3.

(1) 1-Chloro-3-(6-methoxypyridin-3-yl)-2-propyne hydrochloride

(2) 1-Chloro-3-(4-methoxypyridin-3-yl)-2-propyne hydrochloride

Preparation 5

Isobutyl chloroformate (4.4 ml) was added dropwise to a suspension of (E)-3-(3-pyridyl)acrylic acid (5.0 g) and N-methylmorpholine (4.05 ml) in 1,2-dimethoxyethane (50 ml) under -18°C. After being stirred at the same temperature for 0.5 hour, a solution of sodium borohydride (1.86 g) in water (10 ml) was added to the mixture all at once. The resulting mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate as eluent. The fractions containing the objective compound were collected and evaporated under reduced pressure to give (E)-3-(3-pyridyl)-2-propen-1-ol (1.0 g) as an oil.

NMR ($CDCl_3$, δ) : 4.40 (2H, d, J=4.0Hz), 6.52 (1H, dt, J=4.0, 16.1Hz, trans), 6.65 (1H, d, J=16.1Hz, trans), 7.45 (1H, dd, J=5.6, 8.0Hz), 7.89 (1H, d, J=8.0Hz), 8.44 (1H, d, J=5.6Hz), 8.58 (1H, s)

MASS : 136 $(M+H)^+$

Preparation 6

Methane sulfonyl chloride (0.22 ml) was added to a mixture of (E)-3-(3-pyridyl)-2-propen-1-ol (0.36 g) and triethylamine (0.74 ml) in dichloromethane (5 ml) under -10°C. After being stirred at the same temperature for 0.5

hour, the reaction mixture was washed with saturated sodium bicarbonate, dried over magnesium sulfate and evaporated under reduced pressure to give (E)-3-(3-pyridyl)-2-propen-1-yl methanesulfonate.

The crude mesylate was used at next step without further purification.

Preparation 7

4-(3-Pyridyl)-3-butyn-1-yl methanesulfonate was obtained according to a similar manner to that of Preparation 6.

Preparation 8

The solution of 3-(3-pyridyl)-2-propyl-1-ol (300 mg) in methanol was hydrogenated using Lindlar catalyst for 4 hours at atmospheric pressure. After removal of catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate as eluent. The fractions containing the objective compound were collected and evaporated under reduced pressure to give (Z)-3-(3-pyridyl)-2-propen-1-ol (50 mg) as an oil.

IR (Nujol) : 3600-2700, 1590, 1575, 1480 cm^{-1}

NMR ($CDCl_3$, δ) : 4.42 (2H, dd, J=1.6, 6.4Hz), 6.04 (1H, dd, J=6.4, 12.0Hz, cis), 6.52 (1H, d, J=12.0Hz, cis), 7.25-7.31 (1H, m), 7.55 (1H, d, J=8.0Hz), 8.30-8.70 (2H, br s)

MASS : 136 $(M+H)^+$

Preparation 9

A mixture of 4-formyl-1-methylimidazole (3.0 g) and triethylphosphonoacetate (6.3 g) in N,N-dimethylformamide (30 ml) was stirred under ice-cooling. After several minutes, sodium hydride (1.63 g, 60% in mineral oil) was added to the mixture, which was stirred for 30 minutes at the same temperature. The resulting mixture was poured into ice-

water, neutralized with aqueous ammonium acetate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give ethyl (E)-3-(1-methyl-1H-imidazol-4-yl)acrylate (4.63 g).

IR (Nujol) : 2900, 1700, 1625 cm^{-1}

NMR ($CDCl_3$, δ) : 1.31 (3H, t, J=7.1Hz), 3.70 (3H, s), 4.23 (2H, q, J=7.1Hz), 6.53 (1H, d, J=15.6Hz), 7.07 (1H, s), 7.45 (1H, s), 7.54 (1H, d, J=15.6Hz)

MASS : 181 $(M+H)^+$

Preparation 10

A solution of ethyl (E)-3-(1-methyl-1H-imidazol-4-yl)acrylate (2.5 g) in tetrahydrofuran (100 ml) was hydrogenated over 10% palladium activated carbon (0.2 g) at room temperature under 2 atmospheric pressure. After removal of catalyst by filtration through Celite pad, the filtrate was concentrated under reduced pressure to give ethyl 3-(1-methyl-1H-imidazol-4-yl)propionate (2.63 g).

IR (Neat) : 2900, 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.24 (3H, t, J=7.1Hz), 2.62 (2H, t, J=7.4Hz), 2.89 (2H, t, J=7.4Hz), 3.62 (3H, s), 4.16 (2H, q, J=7.1Hz), 6.64 (1H, s), 7.33 (1H, s)

MASS : 183 $(M+H)^+$

Preparation 11

To an ice-cooled solution of ethyl 3-(1-methyl-1H-imidazol-4-yl)propionate (2.63 g) in tetrahydrofuran (26 ml) was added lithium aluminum hydride (0.55 g) by small portions under nitrogen atmosphere. After the mixture was stirred for 0.5 hour, water and 15% aqueous sodium hydroxide solution were added successively to the mixture. The resulting precipitates were filtrated off through Celite pad and the filtrate was extracted with ethyl acetate. The organic layer was washed with water and brine successively, dried over

magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using dichloromethane-methanol (100:1) as eluent to give 3-(1-methyl-1H-imidazol-4-yl)-1-propanol (940 mg).

IR (Neat) : 3250, 2900 cm^{-1}

NMR ($CDCl_3$, δ) : 1.86 (2H, m), 2.69 (2H, t, J=6.7Hz), 3.63 (3H, s), 3.73 (2H, t, J=6.0Hz), 6.62 (1H, s), 7.34 (1H, s)

MASS : 141 $(M+H)^+$

Preparation 12

To a solution of oxalyl chloride (0.361 ml) in dichloromethane (10 ml) cooled below -65°C with a dry ice-acetone bath, a solution of dimethyl sulfoxide (0.381 ml) in dichloromethane (1 ml) was added with efficient stirring over 10 minutes. After 20 minutes below -65°C, a solution of 3-(1-methyl-1H-imidazol-4-yl)-1-propanol in dichloromethane (2 ml) was added to the mixture over 10 minutes below -65°C and the mixture was stirred at the same temperature for 20 minutes and then at -45°C ~ -40°C for 30 minutes. After addition of triethylamine (1.0 ml) dropwise to the mixture over 1 minute followed by stirring for 30 minutes, the reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using dichloromethane-methanol (20:1) as eluent to give 3-(1-methyl-1H-imidazol-4-yl)propanol (103 mg).

IR (Neat) : 1715 cm^{-1}

NMR ($CDCl_3$, δ) : 2.85 (4H, m), 3.63 (3H, s), 6.63 (1H, s), 7.34 (1H, s), 9.83 (1H, s)

MASS : 139 $(M+H)^+$

Preparation 13

The following compound was obtained according to a similar manner to that of Preparation 12.

4-Formyl-1-(triphenylmethyl)pyrazole

NMR (DMSO-d_6, δ) : 7.05-7.10 (6H, m), 7.36-7.41 (9H, m), 8.15 (2H, s), 9.81 (1H, s)

Preparation 14

To a solution of (3R)-4-benzyl-3-(hydroxymethyl)-morpholine (13.67 g) in methanol (140 ml) and water (10 ml) was added ammonium formate (10.4 g) and palladium on activated carbon (50%, 1.4 g). The resulting mixture was stirred at 60°C for 3 hours. After removal of insoluble material by filtration, the filtrate was concentrated under reduced pressure to give crude amine (16.43 g). To a solution of the obtained amine in tetrahydrofuran (160 ml) were added triethylamine (32.2 ml) and di-tert-butyl dicarbonate (50.4 g) at 0°C. After stirring at room temperature for 12 hours, the mixture was quenched with water and extracted with ethyl acetate three times. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give crude oil which was purified by column chromatography on a silica gel using a mixture of ethyl acetate and hexane (6:4) as eluent to give (3R)-4-(tert-butoxycarbonyl)-3-(hydroxymethyl)morpholine (8.64 g) as a colorless solid.

NMR ($CDCl_3$, δ) : 1.47 (9H, s), 3.16-3.24 (1H, m), 3.40-3.61 (2H, m), 3.71-4.00 (6H, m)

Preparation 15

The following compound was obtained according to a similar manner to that of Preparation 14.

(2R,2S)-4-(tert-Butoxycarbonyl)-2-(hydroxymethyl)-morpholine

IR (Neat) : 1695 cm^{-1}

NMR ($CDCl_3$, δ) : 1.47 (9H, m), 2.03 (1H, t, J=6.7Hz), 2.70-3.00 (2H, m), 3.45-3.74 (4H, m), 3.84-3.95

(3H, m)

Preparation 16

The following compounds were obtained according to a similar manner to that of Preparation 12.

(1) (3S)-4-(tert-Butoxycarbonyl)-3-formylmorpholine
IR (KBr) : 1734, 1695 cm^{-1}
NMR ($CDCl_3$, δ) : 1.47 (9H, s), 3.00-3.30 (1H, m), 3.48 (1H, dt, J=2.8, 11.7Hz), 3.67 (1H, dt, J=4.2, 12.1Hz), 3.60-3.90 (2H, m), 4.25-4.50 (2H, m), 9.66 (1H, s)

(2) (2R,2S)-4-(tert-Butoxycarbonyl)-2-formylmorpholine
IR (Neat) : 1737, 1681 cm^{-1}
NMR ($CDCl_3$, δ) : 1.47 (9H, m), 2.80-5.00 (7H, m), 9.65 (1H, m)

Preparation 17

The following compounds were obtained according to a similar manner to that of Preparation 9.

(1) Ethyl (2E)-3-[(3R)-4-(tert-butoxycarbonyl)morpholin-3-yl]acrylate
IR (Neat) : 2978, 1716, 1697 cm^{-1}
NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7.4Hz), 1.46 (9H, s), 3.16 (1H, dt, J=3.7, 13.2Hz), 3.49 (1H, dt, J=2.9, 11.9Hz), 3.69 (1H, dd, J=3.6, 11.7Hz), 3.80-3.99 (3H, m), 4.21 (2H, q, J=7.1Hz), 4.50-4.60 (1H, m), 5.93 (1H, dd, J=1.8, 15.9Hz), 6.99 (1H, dd, J=5.3, 15.9Hz)

(2) Ethyl (2E)-3-[(2R,2S)-(4-tert-butoxycarbonyl)morpholin-2-yl]acrylate
IR (Neat) : 1737, 1681 cm^{-1}

NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=3.3Hz), 1.47 (9H, s), 2.30-3.10 (3H, m), 3.57 (1H, dt, J=2.7, 11.3Hz), 3.80-4.20 (3H, m), 4.21 (2H, q, J=7.1Hz), 6.12 (1H, dd, J=1.7, 15.8Hz), 6.83 (1H, dd, J=4.2, 15.8Hz)

Preparation 18

To a solution of ethyl (2E)-3-[(3R)-4-(tert-butoxycarbonyl)morpholin-3-yl]acrylate (1.0 g) in toluene (10 ml) was added diisobutylaluminum hydride (1.02 M in toluene, 7.6 ml) at -78°C ~ -40°C. After stirring for 2 hours at 0°C, the mixture was quenched with methanol (1.2 ml), and stirred for 1 hour at room temperature. After the resulting precipitate was filtered off, the filtrate was evaporated and purified by column chromatography on a silica gel using a mixture of ethyl acetate and hexane (3:7 ~ 4:6) as eluent to give (3R)-4-(tert-butoxycarbonyl)-3-[(E)-3-hydroxy-1-propenyl]morpholine (0.71 g) as a colorless oil.

IR (Neat) : 1691 cm^{-1}

NMR ($CDCl_3$, δ) : 1.47 (9H, s), 3.17 (1H, dt, J=3.7, 12.2Hz), 3.48 (1H, dt, J=2.7, 11.3Hz), 3.65 (1H, dd, J=3.4, 11.6Hz), 3.70-3.91 (3H, m), 4.17-4.19 (2H, m), 4.40-4.50 (1H, m), 5.82-5.93 (2H, m)

Preparation 19

The following compound was obtained according to a similar manner to that of Preparation 18.

(2R,2S)-4-(tert-Butoxycarbonyl)-2-[(E)-3-hydroxy-1-propenyl]morpholine

NMR ($CDCl_3$, δ) : 1.47 (9H, s), 2.62-3.00 (2H, m), 3.56 (1H, dt, J=2.7, 11.4Hz), 3.81-3.94 (4H, m), 4.18 (2H, d, J=5.0Hz), 5.64-6.04 (2H, m)

Preparation 20

The following compounds were obtained according to a

similar manner to that of Preparation 6.

(1) (3R)-4-(tert-Butoxycarbonyl)-3-[(E)-3-methanesulfonyl-oxy-1-propenyl]morpholine

NMR ($CDCl_3$, δ) : 1.47 (9H, s), 3.02 (3H, s), 3.10-3.25 (1H, m), 3.48 (1H, dt, J=2.8, 11.5Hz), 3.63-3.93 (4H, m), 4.45-4.55 (1H, m), 4.74 (2H, d, J=6.2Hz), 5.75-5.86 (1H, m), 6.05 (1H, dd, J=5.5, 15.6Hz)

(2) (2R,2S)-4-(tert-Butoxycarbonyl)-2-[(E)-3-methane-sulfonyloxy-1-propenyl]morpholine

NMR ($CDCl_3$, δ) : 1.47 (9H, m), 2.60-2.72 (1H, m), 2.89-3.02 (1H, m), 3.02 (3H, s), 3.55 (1H, dt, J=2.7, 11.4Hz), 3.82-4.00 (4H, m), 4.73 (2H, d, J=5.1Hz), 5.79-6.01 (2H, m)

Preparation 21

To a mixture of 1-amino-1-cyclopropanemethanol hydrochloride (1.1 g), benzaldehyde (945 mg) and triethylamine (1.24 ml) in 1,2-dichloroethane (10 ml), sodium triacetoxyborohydride (5.66 g) was added with ice-cooling over 5 minutes. After being stirred at room temperature for 13 hours, the mixture was poured into aqueous sodium bicarbonate solution and stirred for several hours. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure to give 1-(N-benzylamino)-1-cyclopropanemethanol (641 mg).

IR (Nujol) : 3300-2700 cm^{-1}

NMR ($CDCl_3$, δ) : 0.50-0.77 (4H, m), 3.51 (2H, s), 3.84 (2H, s), 7.19-7.36 (5H, s)

MASS : 178 $(M+H)^+$

Preparation 22

The following compound was obtained according to a similar manner to that of Preparation 19.

(2S)-2-(N-Benzylamino)-4-methyl-1-pentanol

NMR ($CDCl_3$, δ) : 0.84-0.94 (6H, m), 1.17-1.70 (3H, m), 2.72-2.81 (1H, m), 3.28 (1H, dd, J=6.0, 10.6Hz), 3.66 (1H, dd, J=3.9, 10.6Hz), 3.78 (2H, s), 7.20-7.38 (5H, m)

MASS : 208 $(M+H)^+$

Preparation 23

Chloroacetyl chloride (421 mg) was added dropwise to a mixture of 1-(N-benzylamino)-1-cyclopropanemethanol (600 mg) and powdered potassium carbonate (702 mg) in dichloromethane (6 ml) with ice-cooling and then the mixture was stirred at room temperature for 2 hours. The resulting mixture was washed with diluted hydrochloric acid and brine successively, and concentrated under reduced pressure. A mixture of the oil obtained by the above procedure and potassium tert-butoxide (380 mg) in tert-butanol (6 ml) was stirred for 2 hours under reflux. After being cooled to room temperature, the mixture was diluted with ethyl acetate (10 ml). The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved with ethyl acetate and the ethyl acetate solution was washed with diluted hydrochloric acid and brine successively, dried over magnesium sulfate and concentrated under reduced pressure to give a solid of 4-benzyl-5-spiro-cyclopropyl-3-morpholinone (695.3 mg).

IR (KBr) : 3100-2800, 1643 cm^{-1}

NMR (DMSO-d_6, δ) : 0.64-1.02 (4H, m), 3.69 (2H, s), 4.43 (2H, s), 4.45 (2H, s), 7.17-7.37 (2H, m)

MASS : 218 $(M+H)^+$

Preparation 24

The following compound was obtained according to a similar manner to that of Preparation 21.

(5S)-4-Benzyl-5-(2-methylpropyl)-3-morpholinone

IR (Neat) : 1655 cm^{-1}

NMR ($CDCl_3$, δ) : 0.83 (3H, d, J=6.3Hz), 0.95 (3H, d, J=6.4Hz), 1.33-1.60 (2H, m), 1.79-1.92 (1H, m), 3.08-3.17 (1H, m), 3.56-3.79 (1H, m), 3.82 (2H, d, J=15.0Hz), 4.23 and 4.27 (2H, ABq, J=16.7Hz), 5.47 (1H, d, J=14.9Hz), 7.24-7.39 (5H, m)

MASS : 248 $(M+H)^+$

Preparation 25

A solution of 4-benzyl-5-spirocyclopropyl-3-morpholinone (695.3 mg) in tetrahydrofuran (8 ml) was added dropwise to an ice-cooled suspension of lithium aluminum hydride (112 mg) in tetrahydrofuran (5 ml) over 20 minutes and then the mixture was stirred at 50°C for 2 hours under nitrogen atmosphere. After being cooled to room temperature, sodium fluoride (495 mg) was added to the mixture. The mixture was stirred vigorously and cooled with ice-bath. Water (0.16 ml) was added thereto and the mixture was filtered. The filtrate was concentrated under reduced pressure to give an oil. The oil was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate as eluent to give 4-benzyl-3-(spirocyclopropyl)morpholine (334.8 mg). 4-Benzyl-3-(spirocyclopropyl)morpholine in ethanol (8 ml) was hydrogenated over palladium hydroxide on carbon for 2 hours at atmospheric pressure. After removal of the catalyst by filtration, the filtrate was treated with 4N hydrogen chloride in ethyl acetate (2 ml) and concentrated under reduced pressure to give 3-(spirocyclopropyl)morpholine hydrochloride (81 mg).

IR (KBr) : 3350, 3000-2400 cm^{-1}

NMR ($CDCl_3$, δ) : 0.84-1.10 (4H, m), 3.75 (2H, s), 3.90-4.10 (4H, m), 10.11 (1H, br s)

MASS : 114 $(M+H)^+$ (free)

Preparation 26

The following compound was obtained according to a similar manner to that of Preparation 23.

(3S)-4-Benzyl-3-(2-methylpropyl)morpholine

NMR ($CDCl_3$, δ) : 0.89 (3H, d, J=6.2Hz), 0.93 (3H, d, J=6.3Hz), 1.20-1.40 (1H, m), 1.46-1.61 (2H, m), 2.17-2.27 (1H, m), 2.40-2.50 (1H, m), 2.59-2.68 (1H, m), 3.16 (1H, d, J=13.3Hz), 3.40 (1H, dd, J=11.2, 7.8Hz), 3.59-3.83 (3H, m), 4.04 (1H, d, J=13.3Hz), 7.21-7.36 (5H, m)

MASS : 234 $(M+H)^+$

Preparation 27

The following compound was obtained according to a similar manner to that of Preparation 23.

(3S)-3-(2-Methylpropyl)morpholine hydrochloride

NMR (DMSO-d_6, δ) : 0.87 (3H, s), 0.90 (3H, s), 1.26-1.52 (2H, m), 1.65-1.78 (1H, m), 3.12-3.48 (4H, m), 3.69 (1H, dt, J=3.4, 12.3Hz), 3.87-3.95 (2H, m)

MASS : 144 $(M+H)^+$ (free)

Preparation 28

A solution of 2-amino-5-bromopyridine (5.0 g) and di-tert-butyl dicarbonate (6.39 g) in tert-butanol (100 ml) was stirred at room temperature for 15 hours. The resulting suspension was concentrated under reduced pressure and the residue was chromatographed on a silica gel using dichloromethane eluent. The fractions containing the objective compound were collected and concentrated under reduced pressure to give 2-(tert-butoxycarbonylamino)-5-bromopyridine (3.25 g).

IR (Nujol) : 3210, 1720, 1580, 1525, 1460, 1370 cm^{-1}

NMR ($CDCl_3$, δ) : 1.56 (9H, s), 7.76 (1H, dd, J=2.5, 8.9Hz), 7.95 (1H, d, J=8.9Hz), 8.38 (1H, d, J=2.5Hz), 8.93 (1H, br s)

Preparation 29

To a solution of (2R)-4-benzyl-1-(3,5-dichlorobenzoyl)-2-(3,4-dimethylbenzyl)piperazine (5.03 g) in dichloromethane (50 ml) was added 1-chloroethyl chloroformate (1.51 ml) slowly at 0°C, and then the mixture was heated at reflux under stirring. After 5.5 hours, the solvent was removed in vacuo and then the resulting residue was dissolved in methanol (20 ml) and refluxed for 0.5 hour. After removal of the solvent, the resulting residue was triturated with isopropyl ether to afford (2R)-1-(3,5-dichlorobenzoyl)-2-(3,4-dimethylbenzyl)piperazine hydrochloride (4.84 g).

IR (Nujol) : 3350, 1625 cm^{-1}

NMR (DMSO-d_6, δ) : 2.10-4.60 (15H, m), 6.50-9.70 (6H, m)

MASS : 377 $(M+H)^+$ (free)

Preparation 30

The following compounds were obtained according to a similar manner to that of Preparation 29.

(1) (2R)-1-(3,5-Dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]-piperazine hydrochloride

IR (KBr) : 1637 cm^{-1}

NMR (DMSO-d_6, δ) : 2.80-4.80 (9H, m), 6.80-10.20 (8H, m)

MASS : 388 $(M+H)^+$ (free)

(2) (2R)-1-(3,5-Dichlorobenzoyl)-2-(2-naphthylmethyl)-piperazine hydrochloride

NMR (DMSO-d_6, δ) : 2.80-4.70 (9H, m), 6.50-8.00 (10H, m)

MASS : 399 $(M+H)^+$ (free)

(3) (2R)-1-(3,5-Dichlorobenzoyl)-2-[4-(trifluoromethyl)-

benzyl]piperazine dihydrochloride

IR (KBr) : 3430, 2930, 2790, 1648, 1164 cm^{-1}

NMR (DMSO-d_6, δ) : 2.70-5.30 (9H, m), 6.50-7.90 (7H, m), 9.62 (1H, br s)

MASS : 417 $(M+H)^+$(free)

(4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)piperazine hydrochloride

IR (KBr) : 3700-3200, 1639, 1281, 1136 cm^{-1}

NMR (DMSO-d_6, δ) : 2.90-3.80 (7H, m), 4.40-5.30 (2H, m), 6.90-8.30 (10H, m)

MASS : 317 $(M+H)^+$ (free)

Preparation 31

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)piperazine fumarate (2 g) was treated with 10% aqueous sodium hydroxide solution (14 ml) and dichloromethane (14 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. A mixture of free piperazine derivative obtained by the above procedure, potassium carbonate (0.76 g) and 1,4-dichloro-2-butyne (0.43 ml) in N,N-dimethylformamide (15 ml) was stirred for 4.5 hours at room temperature. The reaction mixture was poured into water (75 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of toluene and ethyl acetate (10:1) as eluent to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(4-chloro-2-butynyl)-2-(2-naphthylmethyl)piperazine (1.18 g).

IR (Neat) : 3600-3100, 1638, 1275, 1127, 900 cm^{-1}

NMR ($CDCl_3$, δ) : 2.31-5.30 (13H, m), 6.90-7.95 (10H, m)

MASS : 553 $(M+H)^+$

Example 1

(1) A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]piperazine (0.67 g), 1-chloro-3-(3-pyridyl)-2-propyne hydrochloride (0.3 g) and potassium carbonate (0.52 g) in N,N-dimethylformamide (5 ml) was stirred for 5 hours at 50°C. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate as eluent to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(3-pyridyl)-2-propynyl]-piperazine (0.25 g) as a syrup.

(2) The following compound was prepared by treatment of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)-methyl]-4-[3-(3-pyridyl)-2-propynyl]piperazine with 4N hydrochloric acid in ethyl acetate.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(3-pyridyl)-2-propynyl]piperazine dihydrochloride

mp : 180-190°C

$[\alpha]_D^{24.6}$: -10.50° (C=0.1, MeOH)

IR (Nujol) : 3600-3200, 2700-2500, 1643, 1530, 1428, 1361, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 3.20-5.20 (11H, m), 6.40-8.30 (10H, m), 8.74-8.80 (1H, m), 8.85-8.90 (2H, m), 10.90-11.10 (1H, m)

MASS : 571 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{24}F_6N_4O \cdot 2HCl \cdot 1.8H_2O$:
C 53.31, H 4.41, N 8.29
Found : C 53.28, H 4.53, N 7.87

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(6-methoxypyridin-3-yl)-2-propynyl]piperazine dihydrochloride
mp : 160-170°C
$[\alpha]_D^{24.2}$: -14.72° (C=0.55, MeOH)
IR (KBr) : 3600-3300, 2700-2500, 1648, 1617, 1494, 1430, 1280 cm^{-1}
NMR (DMSO-d_6, δ) : 2.05-2.20 (6H, m), 2.80-5.20 (11H, m), 3.90 (3H, s), 6.50-8.40 (9H, m)
MASS : 590 $(M+H)^+$ (free)
Elemental Analysis Calcd. for $C_{31}H_{29}F_6N_3O_2 \cdot 2HCl \cdot 0.5H_2O$: C 55.45, H 4.80, N 6.26
Found : C 55.28, H 4.86, N 6.12

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(6-methoxypyridin-3-yl)-2-propynyl]-piperazine dihydrochloride
mp : 183-189°C
$[\alpha]_D^{23.9}$: -21.0° (C=0.55, MeOH)
IR (KBr) : 3600-3300, 2700-2500, 1644, 1602, 1494, 1428, 1280 cm^{-1}
NMR (DMSO-d_6, δ) : 3.20-5.20 (11H, m), 3.90 (3H, s), 6.60-8.40 (11H, m), 10.95 (1H, br s), 12.00-12.40 (2H, m)
MASS : 600 $(M+H)^+$ (free)
Elemental Analysis Calcd. for $C_{31}H_{26}F_6N_4O_2 \cdot 2HCl \cdot H_2O$: C 53.85, H 4.37, N 8.10
Found : C 53.90, H 4.36, N 8.02

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(2-pyridyl)-2-propynyl]piperazine

Example 3

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(2-pyridyl)-2-propynyl]piperazine dihydrochloride (0.2 g) was made free with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue dissolved in methanol (10 ml) and the solution was hydrogenated over 10% palladium on activated carbon (50 mg) at room temperature under 2-3 atoms. After removal of catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(2-pyridyl)propyl]-piperazine dihydrochloride.

mp : 120-130°C

$[\alpha]_D^{24.5}$: -12.81° (C=0.32, MeOH)

IR (Nujol) : 3600-3300, 2700-2500, 1635, 1450, 1380, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-5.20 (21H, m), 6.60-7.80 (5H, m), 7.80 (1H, d, J=8.0Hz), 7.88 (1H, t, J=7.0Hz), 8.18 (1H, s), 8.49 (1H, t, J=7.1Hz), 8.81 (1H, d, J=5.2Hz), 11.20-12.20 (2H, m)

MASS : 564 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{31}F_6N_3O \cdot 2HCl \cdot 2.7H_2O$: C 52.59, H 5.65, N 6.13

Found : C 52.66, H 5.78, N 5.77

Example 4

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(3-pyridyl)propyl]piperazine dihydrochloride

mp : 150-160°C

$[\alpha]_D^{22.9}$: -2.86° (C=0.42, MeOH)

IR (KBr) : 3600-3000, 2700-2010, 1641, 1554, 1461,

1428, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 2.10-5.20 (15H, m), 6.60-8.30 (9H, m), 8.45-8.55 (1H, m), 8.80-9.00 (2H, m), 10.95-11.05 (1H, m), 11.90-12.00 (2H, br s)

MASS : 575 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{28}F_6N_4O \cdot 2HCl \cdot 1.2H_2O$:
C 50.71, H 5.25, N 7.89
Found : C 50.65, H 5.35, N 7.20

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(2-pyridyl)propyl]piperazine dihydrochloride

mp : 80-100°C

$[\alpha]_D^{23.1}$: -5.29° (C=0.86, MeOH)

IR (KBr) : 3600-3300, 2700-2500, 1637, 1617, 1460, 1282 cm^{-1}

NMR (DMSO-d_6, δ) : 2.20-2.40 (2H, m), 3.10-5.20 (13H, m), 6.60-8.30 (10H, m), 8.49 (1H, d, J=7.8Hz), 8.80 (1H, d, J=5.0Hz), 10.90-11.05 (1H, br s)

MASS : 575 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{28}F_6N_4O \cdot 2HCl \cdot 1.2H_2O$:
C 53.85, H 4.88, N 8.37
Found : C 53.92, H 5.30, N 7.66

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[4-(3-pyridyl)butyl]piperazine dihydrochloride

mp : 140-145°C

$[\alpha]_D^{22.3}$: -8.33° (C=0.30, MeOH)

IR (Nujol) : 3600-3000, 2700-2300, 1641, 1465, 1430, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 1.60-5.20 (17H, m), 6.60-9.00 (12H, m), 11.00 (1H, br s), 11.59 (2H, br s)

MASS : 589 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{30}F_6N_4O \cdot 2HCl \cdot 2H_2O$:

C 53.38, H 5.20, N 8.03

Found : C 53.47, H 5.28, N 7.51

Example 5

(1) Methanesulfonyl chloride (0.094 ml) was added to a mixture of (Z)-3-(3-pyridyl)-2-propen-1-ol (0.15 g) and triethylamine (0.2 ml) in dichloromethane (2 ml) under -10°C. After being stirred at the same temperature for 0.5 hour, the reaction mixture was washed with saturated sodium bicarbonate, dried over magnesium sulfate and evaporated under reduced pressure. The obtained mesylate was added to a mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]piperazine (0.5 g), powdered potassium carbonate (0.61 g) and catalytic amount of potassium iodide in a mixed solvent of acetonitrile (10 ml) and N,N-dimethylformamide (2 ml). The resulting mixture was stirred at 50°C for 1.5 hours and then filtered. The filtrate was evaporated under reduced pressure and the resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol as eluent. The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[(Z)-3-(3-pyridyl)-2-propenyl]piperazine (0.49 g) as a syrup.

NMR ($CDCl_3$, δ) : 1.80-5.20 (11H, m), 5.97 (1H, dt, J=6.6, 11.7Hz, cis), 6.60 (1H, d, J=11.7Hz, cis), 6.80-8.00 (10H, m), 8.23 (1H, s), 8.45-8.60 (2H, m)

MASS : 562 $(M+H)^+$

(2) The following compound was prepared by treatment of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)-methyl]-4-[(Z)-3-(3-pyridyl)-3-propenyl]piperazine with 4N hydrogen chloride in ethyl acetate.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-

yl)methyl]-4-[(Z)-3-(3-pyridyl)-2-propenyl]piperazine dihydrochloride

mp : 165-177°C

$[\alpha]_D^{22.9}$: +14.9° (C=0.50, MeOH)

IR (KBr) : 3600-3300, 2700-2500, 1641, 1457, 1427, 1359, 1280, 1184 cm^{-1}

NMR (DMSO-d_6, δ) : 3.00-5.20 (11H, m), 6.40-8.40 (12H, m), 8.70-8.85 (2H, m), 11.05 (1H, br s), 12.00 (2H, m)

MASS : 573 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{26}F_6N_4O \cdot 2HCl \cdot 2.5H_2O$: C 52.18, H 4.82, N 8.11

Found : C 52.34, H 4.73, N 8.01

Example 6

The following compounds were obtained according to a similar manner to that of Example 5.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[(E)-3-(3-pyridyl)-2-propenyl]-piperazine dihydrochloride

mp : 170-174°C

$[\alpha]_D^{24.1}$: -8.50° (C=0.20, MeOH)

IR (KBr) : 3600-3300, 2700-2500, 1643, 1554, 1432, 1367, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-2.30 (6H, m), 2.80-5.20 (6H, m), 6.60-9.05 (12H, m)

MASS : 562 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{29}F_6N_3O \cdot 2HCl \cdot 2.0H_2O$: C 53.74, H 5.26, N 6.27

Found : C 53.71, H 5.33, N 5.83

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[4-(3-pyridyl)-3-butynyl]piperazine

NMR ($CDCl_3$, δ) : 2.20-5.20 (13H, m), 6.80-8.00 (10H,

m), 8.15 (1H, s), 8.49 (1H, d, J=3.8Hz), 8.64 (1H, br s)

MASS : 585 $(M+H)^+$

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(1H-pyrazol-1-yl)propyl]piperazine hydrochloride

mp : 73-75°C

$[\alpha]_D^{24.7}$: -17.30° (C=0.50, MeOH)

IR (KBr) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 1.85-5.20 (21H, m), 6.20-8.30 (9H, m)

MASS : 553 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{28}H_{31}ClF_6N_4O \cdot 2H_2O$:
C 53.80, H 5.64, N 8.96

Found : C 53.67, H 5.56, N 7.83

Example 7

The following compounds were obtained according to a similar manner to that of Example 5-(2).

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(2-pyridyl)-2-propynyl]piperazine dihydrochloride

mp : 160-166°C

$[\alpha]_D^{24.7}$: -16.80° (C=0.50, MeOH)

IR (KBr) : 3600-3200, 2700-2500, 1643, 1540, 1380, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 3.20-5.20 (11H, m), 6.60-8.30 (11H, m), 8.65 (1H, d, J=2.7Hz), 10.90-11.05 (1H, m)

MASS : 571 $(M+H)^+$ (free), 607

Elemental Analysis Calcd. for $C_{30}H_{24}F_6N_4O \cdot 2HCl \cdot 1.5H_2O$:
C 53.74, H 4.36, N 8.36

Found : C 53.73, H 4.66, N 7.71

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[4-(3-pyridyl)-3-butynyl]piperazine

dihydrochloride

mp : 175-185°C

$[\alpha]_D^{21.7}$: -10.30° (C=0.50, MeOH)

IR (KBr) : 3600-3300, 2700-2500, 1641, 1459, 1428, 1368, 1282 cm^{-1}

NMR (DMSO-d_6, δ) : 3.20-5.20 (13H, m), 6.60-8.30 (9H, m), 8.65-8.85 (2H, m), 10.99 (1H, s), 11.90-12.10 (2H, m)

MASS : 585 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{26}F_6N_4O \cdot 2HCl \cdot 1.2H_2O$:
C 54.83, H 4.51, N 8.25
Found : C 54.79, H 4.87, N 7.67

Example 8

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-(4-chloro-2-butynyl)piperazine (0.25 g), (R)-2-(methoxymethyl)pyrrolidine (0.10 g), potassium carbonate (0.25 g) and potassium iodide (10 mg) in dry N,N-dimethylformamide (5 ml) was stirred for 5 hours at room temperature. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate as eluent and treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[4-[(2R)-2-(methoxymethyl)-pyrrolidino]-2-butynyl]piperazine dihydrochloride (0.19 g).

mp : 190-195°C

$[\alpha]_D^{24.8}$: +9.3° (C=0.50, MeOH)

IR (Nujol) : 3600-3300, 2700-2500, 1641, 1552, 1428, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 1.6-2.40 (4H, m), 3.10-5.20 (18H, m), 6.60-8.30 (8H, m), 11.50-11.70 (3H, m)

MASS : 621 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{32}H_{34}F_6N_4O_2 \cdot 2HCl \cdot 1.5H_2O$:
C 53.34, H 5.46, N 7.78
Found : C 53.35, H 5.54, N 7.60

Example 9

To a mixture of 3,5-dichlorobenzoic acid (2.6 g), (3R)-1-benzyl-3-(3,4-dimethylbenzyl)piperazine dihydrochloride (5.0 g) and triethylamine (8.54 ml) in dichloromethane (80 ml) was added 2-chloro-1-methylpyridinium iodide (3.83 g) under ice-cooling, and then the mixture was stirred at room temperature for 1 hour. The mixture was evaporated under reduced pressure, and the resulting residue was dissolved into ethyl acetate. The ethyl acetate solution was filtrated and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using hexane-ethyl acetate (10:1) as eluent to give (2R)-4-benzyl-1-(3,5-dichlorobenzoyl)-2-(3,4-dimethylbenzyl)piperazine (5.58 g).

IR (Nujol) : 2500, 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 1.90-2.30 (8H, m), 2.55-4.80 (9H, m), 6.50-7.15 (5H, m), 7.20-7.40 (5H, m), 7.59 (1H, br)

MASS : 467 $(M+H)^+$

Example 10

The following compound was obtained according to a similar manner to that of Example 9.

(2R)-4-Benzyl-1-(3,5-dichlorobenzoyl)-2-[4-(trifluoromethyl)benzyl]piperazine

IR (Neat) : 2942, 2809, 1641, 1070 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-4.90 (11H, m), 6.59 (1H, s), 7.10-7.70 (11H, m)

MASS : 507 $(M+H)^+$

Example 11

To a solution of (3R)-1-benzyl-3-(2-naphthylmethyl)piperazine (3.23 g) and triethylamine (4.3 ml) in dichloromethane (60 ml) was added a solution of 3,5-dichlorobenzoyl chloride (6.0 g) in dichloromethane (10 ml) at 0°C. After stirring at room temperature for 3 hours, the mixture was quenched with water and extracted three times with ethyl acetate. The combined extracts were dried over magnesium sulfate, and evaporated under reduced pressure. The obtained residue was triturated with a mixture of dichloromethane and hexane to give (2R)-4-benzyl-1-(3,5-dichlorobenzoyl)-2-(2-naphthylmethyl)-piperazine.

NMR (DMSO-d_6, δ) : 3.00-4.70 (9H, m), 6.66-7.86 (17H, m)

MASS : 689 $(M+H)^+$ (free)

Example 12

The following compound was obtained according to a similar manner to that of Example 11.

(2R)-4-Benzyl-1-(3,5-dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]piperazine

NMR (DMSO-d_6, δ) : 2.10-4.60 (9H, m), 5.76 (2H, s), 6.70-7.68 (13H, m)

MASS : 388 $(M+H)^+$ (free)

Example 13

The following compound was obtained according to a similar manner to that of Example 1-(1).

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine dihydrochloride

mp : 140-150°C

$[\alpha]_D^{25.9}$: -9.2° (C=0.50, MeOH)

IR (KBr) : 3700-3200, 3000-2300, 1644, 1550, 1428, 1367, 1280 cm^{-1}

NMR (DMSO-d_6, δ): 2.20-5.20 (11H, m), 7.00-8.65 (14H, m)

MASS : 582 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{25}F_6N_4O \cdot 2HCl \cdot 2.57H_2O$: C 54.85, H 4.62, N 6.00

Found : C 54.85, H 4.56, N 5.86

Example 14

(1) Lindlar catalyst (Pd-$CaCO_3$-PbO) (86 mg) was added to a solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine in methanol (20 ml). The mixture was stirred for 2 hours under hydrogen at 25°C and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was chromatographed on silica gel using a mixed eluent of hexane and ethyl acetate. The faster eluting fractions were collected, concentrated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)-4-[(2Z)-3-(3-pyridyl)-2-propenyl]piperazine dihydrochloride.

mp : 130-150°C

$[\alpha]_D^{27.5}$: -25.20° (C=0.25, MeOH)

IR (KBr) : 3700-2200, 1646, 1280 cm^{-1}

NMR (DMSO-d_6, δ): 2.00-5.20 (11H, m), 6.30-8.90 (16H, m)

MASS : 584 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{32}H_{27}F_6N_3O \cdot 2HCl \cdot 3.7H_2O$: C 53.19, H 5.07, N 5.82

Found : C 53.19, H 5.21, N 5.61

(2) The slower eluting fractions were collected, concentrated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)-4-[3-(3-pyridyl)propyl]piperazine dihydrochloride.

mp : 138-148°C

$[\alpha]_D^{26.4}$: -28.60° (C=0.25, MeOH)

IR (KBr) : 3700-2200, 1646, 1280, 1135 cm^{-1}

NMR (DMSO-d_6, δ): 2.00-5.20 (15H, m), 6.30-8.90 (14H, m)

MASS : 586 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{32}H_{29}F_6N_3O \cdot 2HCl \cdot 2.9H_2O$:
C 54.10, H 5.22, N 5.92

Found : C 54.11, H 5.37, N 5.70

Example 15

A mixture of (2R)-1-(3,5-dichlorobenzoyl)-2-(3,4-dimethylbenzyl)piperazine hydrochloride (400 mg) and 4-(4-chloro-2-butynyl)morpholine hydrochloride (223 mg) in dried acetonitrile (4.0 ml) was stirred at 50°C in the presence of powdered potassium carbonate (534 mg) and potassium iodide (32 mg). After 3 hours, the reaction mixture was filtered and the insoluble material on the filter was washed with acetonitrile. The filtrate and the washing were combined and then concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and methanol (10:1) as eluent. The product obtained was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-(3,5-dichlorobenzoyl)-2-(3,4-dimethylbenzyl)-4-(4-morpholino-2-butynyl)piperazine dihydrochloride (221 mg).

mp : 175°C (dec.)

$[\alpha]_D^{27.9}$: +6.80° (C=0.50, MeOH)

IR (Nujol) : 2400, 1640, 1120 cm^{-1}

NMR (DMSO-d_6, δ) : 2.10-4.40 (21H, m), 6.69 (3H, br), 7.06 (2H, br), 7.61 (1H, br)

MASS : 514 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{28}H_{33}Cl_2N_3O_2 \cdot 2HCl \cdot 2H_2O$:
C 53.94, H 6.30, N 6.74

Found : C 53.86, H 6.15, N 6.41

Example 16

The following compounds were obtained according to a similar manner to that of Example 15.

(1) (2R)-1-(3,5-Dichlorobenzoyl)-2-(3,4-dimethylbenzyl)-4-(4-thiomorpholino-2-butynyl)piperazine dihydrochloride
mp : 128°C (dec.)
$[\alpha]_D^{28.0}$: +6.40° (C=0.50, MeOH)
IR (Nujol) : 2400, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 2.05-4.70 (21H, m), 6.71 (3H, br), 7.04 (2H, br), 7.61 (1H, br)
MASS : 530 $(M+H)^+$ (free)
Elemental Analysis Calcd. for $C_{28}H_{33}Cl_2N_3OS \cdot 2HCl \cdot 2H_2O$: C 52.59, H 6.15, N 6.57
Found : C 52.72, H 6.19, N 6.35

(2) (2R)-1-(3,5-Dichlorobenzoyl)-2-(3,4-dimethylbenzyl)-4-[(E)-4-morpholino-2-butenyl]piperazine dihydrochloride
mp : >230°C
$[\alpha]_D^{25.3}$: +5.80° (C=0.50, MeOH)
IR (KBr) : 3426, 2927, 1120, 970 cm^{-1}
NMR (DMSO-d_6, δ) : 2.10-4.70 (23H, m), 6.17 (2H, br), 6.69 (3H, br), 7.07 (2H, br), 7.63 (1H, br)
MASS : 516 $(M+H)^+$ (free)
Elemental Analysis Calcd. for $C_{28}H_{37}Cl_4N_3O_2 \cdot 0.5H_2O$: C 56.20, H 6.40, N 7.02
Found : C 56.20, H 6.29, N 6.89

(3) (2R)-1-(3,5-Dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]-4-(4-thiomorpholino-2-butynyl)piperazine dihydrochloride
mp : 175°C (dec.)
$[\alpha]_D^{26.0}$: +26.0° (C=0.50, MeOH)
IR (KBr) : 3407, 2543, 1639 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.10 (21H, m), 6.70-7.80 (8H, m), 11.02 (1H, br s)

MASS : 541 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{28}H_{32}Cl_4N_4OS \cdot 1.5H_2O$:
C 52.43, H 5.50, N 8.73
Found : C 52.34, H 5.60, N 8.42

(4) (2R)-1-(3,5-Dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]-4-(4-morpholino-2-butynyl)piperazine dihydrochloride

mp : 165°C (dec.)

$[\alpha]_D^{26.0}$: +27.50° (C=0.50, MeOH)

IR (KBr) : 3407, 1639, 1126 cm^{-1}

NMR (DMSO-d_6, δ) : 2.80-5.20 (21H, m), 6.70-7.85 (8H, m), 11.00 (1H, br s)

MASS : 525 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{28}H_{32}Cl_4N_4O_2 \cdot 3H_2O$:
C 51.55, H 5.87, N 8.59
Found : C 51.59, H 5.52, N 8.33

(5) (2R)-1-(3,5-Dichlorobenzoyl)-2-(2-naphthylmethyl)-4-(4-thiomorpholino-2-butynyl)piperazine dihydrochloride

mp : 154°C (dec.)

$[\alpha]_D^{23.8}$: -14.10° (C=0.50, MeOH)

IR (KBr) : 3417, 2933, 2537, 1641 cm^{-1}

NMR (DMSO-d_6, δ) : 2.70-5.20 (21H, m), 6.56 (1H, br), 7.08 (1H, br), 7.53 (4H, br), 7.89 (4H, br)

MASS : 552 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{33}Cl_4N_3OS \cdot 1.5H_2O$:
C 55.22, H 5.56, N 6.44
Found : C 55.09, H 5.64, N 6.31

(6) (2R)-1-(3,5-Dichlorobenzoyl)-2-(2-naphthylmethyl)-4-(4-morpholino-2-butynyl)piperazine dihydrochloride

mp : 171°C (dec.)

$[\alpha]_D^{23.3}$: -15.10° (C=0.50, MeOH)

IR (KBr) : 3407, 2931, 2561, 1641, 971 cm^{-1}

NMR (DMSO-d_6, δ) : 3.00-5.20 (21H, m), 6.56 (1H, br),

7.08 (1H, br), 7.53 (4H, br), 7.89 (4H, br)

MASS : 536 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{33}Cl_4N_3O_2 \cdot H_2O$:
C 57.43, H 5.62, N 6.70

Found : C 57.67, H 5.68, N 6.31

(7) (2R)-1-(3,5-Dichlorobenzoyl)-2-[4-(trifluoromethyl)-benzyl]-4-(4-thiomorpholino-2-butynyl)piperazine dihydrochloride

mp : 172°C (dec.)

$[\alpha]_D^{25.4}$: +15.80° (C=0.50, MeOH)

IR (KBr) : 3430, 2917, 2524, 1641, 1068 cm^{-1}

NMR (DMSO-d_6, δ) : 2.70-5.20 (21H, m), 6.69 (1H, s), 7.10-7.30 (2H, m), 7.63 (4H, br)

MASS : 570 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{27}H_{30}Cl_4F_3N_3OS \cdot 0.5H_2O$:
C 49.71, H 4.79, N 6.44

Found : C 49.37, H 5.09, N 6.30

(8) (2R)-1-(3,5-Dichlorobenzoyl)-2-[4-(trifluoromethyl)-benzyl]-4-(4-morpholino-2-butynyl)piperazine dihydrochloride

mp : 186°C (dec.)

$[\alpha]_D^{25.4}$: +17.50° (C=0.50, MeOH)

IR (KBr) : 3421, 2935, 2553, 1644, 1068 cm^{-1}

NMR (DMSO-d_6, δ) : 2.80-5.20 (21H, m), 6.72 (1H, s), 7.10-7.40 (2H, m), 7.64 (4H, br)

MASS : 554 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{27}H_{30}Cl_4F_3N_3O_2 \cdot 0.5H_2O$:
C 50.96, H 4.91, N 6.60

Found : C 50.57, H 5.05, N 6.52

Example 17

A mixture of (2R)-1-(3,5-dichlorobenzoyl)-2-(3,4-dimethylbenzyl)piperazine hydrochloride (300 mg), 3-bromo-1-

propanol (121 mg), potassium carbonate (251 mg) and potassium iodide (24 mg) in dried acetonitrile (3 ml) was stirred at 50°C for 10 hours. After being cooled to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate as eluent to give (2R)-1-(3,5-dichlorobenzoyl)-2-(3,4-dimethylbenzyl)-4-(3-hydroxypropyl)piperazine as a syrup. Methanesulfonyl chloride (58 mg) was added to an ice-cooled solution of the alcohol obtained at above procedure (210 mg) and triethylamine (97.6 mg) in dichloromethane (4 ml) over 1.5 hours. After being stirred for 1 hour, the reaction mixture was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate and evaporated under reduced pressure to give the corresponding mesylate. A mixture of the mesylate obtained by the above procedure, 4-aminomorpholine (59.1 mg) and triethylamine (73.2 mg) in methanol (4 ml) was stirred under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate as eluent and treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-1-(3,5-dichlorobenzoyl)-2-(3,4-dimethylbenzyl)-4-(N-morpholino-3-aminopropyl)piperazine dihydrochloride.

mp : 71°C (dec.)

$[\alpha]_D^{22.5}$: +1.00° (C=0.50, MeOH)

IR (Nujol) : 3400, 2950, 1640, 1100 cm^{-1}

NMR (DMSO-d_6, δ) : 2.10-4.70 (23H, m), 6.68 (3H, br), 7.06 (2H, br), 7.63 (1H, br)

MASS : 519 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{27}H_{38}Cl_4N_4O_2 \cdot 2.5H_2O$:
C 50.87, H 6.80, N 8.79

Found : C 51.03, H 7.15, N 8.84

Example 18

Under nitrogen atmosphere, to a mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)piperazine (315 mg) and 3-(1-methyl-1H-imidazol-4-yl)propanal (98 mg) in dichloromethane (6 ml) was added sodium triacetoxyborohydride (225 mg) and stirred at room temperature. After 4 hours, aqueous sodium bicarbonate solution was added to the mixture and the mixture was stirred for several minutes. The organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using dichloromethane-methanol (10:1) as eluent and treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(1-methyl-1H-imidazol-4-yl)propyl]piperazine dihydrochloride (187.1 mg).

mp : 91°C (dec.)

$[\alpha]_D^{24.2}$: -11.20° (C=0.50, MeOH)

IR (Nujol) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-5.20 (21H, m), 6.67 (1H, br s), 6.90-7.20 (2H, m), 7.44 (1H, br s), 7.56 (1H, br s), 7.67 (1H, br s), 8.18 (1H, br s), 9.03 (1H, br s)

MASS : 567 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{29}H_{34}Cl_2F_6N_4O \cdot 3.5H_2O$:
C 49.58, H 5.88, N 7.97
Found : C 49.71, H 5.90, N 7.79

Example 19

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)piperazine (500 mg), 2-(2-chloroethoxy)-ethanol (168 mg), potassium carbonate (233 mg) and potassium iodide (56 mg) in N,N-dimethylformamide (2 ml) was heated with stirring at 50°C for 17 hours, 60°C for 13 hours and 70°C for 1 hour. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was

washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the resulting residue was purified by column chromatography on silica gel using dichloromethane-methanol (10:1) as eluent to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-(2-hydroxyethoxy)ethyl]piperazine (359 mg).

IR (Neat) : 3450, 1640, 1440, 1280, 1130 cm^{-1}

NMR (DMSO-d_6, δ) : 2.03-4.93 (23H, m), 6.60-8.20 (6H, m)

MASS : 533 $(M+H)^+$

Example 20

To a stirred solution of oxalyl chloride (151 mg) in dichloromethane (3 ml) was added dropwise a solution of dimethylsulfoxide (123 mg) in dichloromethane (0.25 ml) at -78°C under nitrogen atmosphere. After 15 minutes, (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-(2-hydroxyethoxy)ethyl]piperazine (317 mg) was added at the same temperature. After 15 minutes, the resulting mixture was stirred at -45°C for 1 hour. Triethylamine (446 mg) was added at -45°C, and the whole was stirred at 0°C for 20 minutes and then treated with aqueous solution of ammonium chloride (2 ml). The organic layer was separated and dried over magnesium sulfate. After evaporation of the solvent, the resulting residue was purified by column chromatography on silica gel using ethyl acetate as eluent to afford (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-(formylmethoxy)ethyl]piperazine (171 mg).

IR (Neat) : 3450, 1740, 1640, 1440, 1280, 1130 cm^{-1}

NMR (DMSO-d_6, δ) : 1.91-4.91 (22H, m), 6.53-8.20 (6H, m)

MASS : 351 $(M+H)^+$

Example 21

To a stirred mixture of 3,3-dimethylmorpholine hydrochloride (63 mg) and triethylamine (42 mg) in dichloromethane (5 ml) were added (2R)-1-[3,5-

bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-(formylmethoxy)ethyl]piperazine (200 mg) and sodium triacetoxyborohydride (120 mg) at room temperature. The resulting mixture was stirred for 1 hour and then treated with aqueous sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using dichloromethane-methanol (10:1) as eluent and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-[2-(3,3-dimethylmorpholino)ethoxy]ethyl]piperazine dihydrochloride (193 mg) as a powder.

$[\alpha]_D^{23}$: -18.20° (C=0.50, MeOH)

IR (Neat) : 3450, 2600, 1640, 1430, 1280, 1140 cm^{-1}

NMR (DMSO-d_6, δ) : 1.33 (6H, s), 2.04-5.23 (29H, m), 6.60-8.26 (6H, m)

MASS : 630 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{32}H_{41}F_6N_3O_3 \cdot 2HCl \cdot 3.32H_2O$:
C 50.41, H 6.56, N 5.51
Found : C 50.41, H 6.29, N 5.31

Example 22

The following compound was obtained according to a similar manner to that of Example 21.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-(2-morpholinoethoxy)ethyl]piperazine dihydrochloride

$[\alpha]_D^{23}$: -21.4° (C=0.50, MeOH)

IR (Neat): 3450, 2600, 1640, 1430, 1280, 1180, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 2.08-5.20 (31H, m), 6.60-8.24 (6H, m)

MASS : 602 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{37}F_6N_3O_3 \cdot 2HCl \cdot 2.66H_2O$:
C 49.87, H 6.18, N 5.82
Found : C 49.87, H 6.25, N 5.65

Example 23

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-(3-methylsulfonyloxypropyl)-piperazine (250 mg), 4-aminothiomorpholine (90 mg) and sodium carbonate (180 mg) in methanol (5 ml) was stirred at reflux temperature for 3 hours. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-methanol (10:1) as eluent and treated with 4N hydrogen chloride in ethyl acetate (3 ml) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)-methyl]-4-[3-(thiomorpholinoamino)propyl]piperazine dihydrochloride (62 mg) as a powder.

$[\alpha]_D^{27}$: -5.80° (C=0.50, MeOH)

IR (Neat) : 3300, 2500, 1630, 1420, 1275, 1130 cm^{-1}

NMR (DMSO-d_6, δ) : 2.03-5.20 (23H, m), 6.60-8.24 (8H, m), 10.95 (1H, s)

MASS : 614 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{29}H_{35}Cl_2F_6N_5OS \cdot 3H_2O$:
C 47.10, H 5.37, N 8.88

Found : C 47.03, H 5.58, N 9.46

Example 24

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(2-methylsulfonyloxyethyl)piperazine (200 mg), 3-hydroxymethylpiperidine (44 mg) and triethylamine (73 mg) in methanol (5 ml) was stirred at reflux temperature for 2.5 hours. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (30 ml) and water (10 ml). The organic layer was dried over magnesium sulfate and then evaporated under reduced pressure. The obtained residue was purified by column chromatography on silica gel using dichloromethane-methanol (10:1) as eluent and treated with 4N hydrogen chloride in ethyl acetate (0.2 ml) to give (2R)-1-[3,5-bis-

(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-(3-hydroxymethylpiperidino)ethyl]piperazine dihydrochloride (85 mg).

$[\alpha]_D^{25}$: -5.30° (C=0.50, MeOH)

IR (Neat) : 3350, 2500, 1640, 1420, 1280, 1180, 1130 cm^{-1}

NMR (DMSO-d_6, δ) : 1.0-5.20 (30H, m), 6.66-8.31 (6H, m)

MASS : 586 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{39}Cl_2F_6N_3O_2 \cdot 3H_2O$:
C 50.58, H 6.36, N 5.90
Found : C 50.58, H 6.24, N 5.87

Example 25

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(4-chloro-2-butynyl)-2-(2-naphthylmethyl)piperazine (600 mg), 3,3-dimethylmorpholine hydrochloride (197 mg) and potassium carbonate (420 mg) in N,N-dimethylformamide (10 ml) was stirred at room temperature in the presence of potassium iodide (10 mg) for 2 days. The reaction mixture was partitioned between ethyl acetate (50 ml) and water (100 ml) and the organic layer was separated, washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using a mixture of ethyl acetate-hexane (10:1). The obtained product was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(3,3-dimethylmorpholino)-2-butynyl]-2-(2-naphthylmethyl)piperazine dihydrochloride (360 mg).

IR (KBr) : 3401, 2929, 2578, 2512, 1644, 1284, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 1.32 (3H, s), 1.39 (3H, s), 3.0-5.4 (19H, m), 7.0-8.2 (10H, m)

MASS : 632 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{34}H_{37}Cl_2F_6N_3O_2 \cdot 2.5H_2O$:
C 54.48, H 5.65, N 5.61

Found : C 54.25, H 5.53, N 5.39

Example 26

Acetic anhydride (209 mg) was added to formic acid (94 mg). The resulting mixture was allowed to warm at 50°C for 30 minutes and then added to (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(morpholinoamino)propyl]piperazine (200 mg) at room temperature. The whole was stirred overnight and then evaporated under reduced pressure. The obtained residue was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate (0.2 ml) to give (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)-4-[(3-(N-formyl-morpholinoamino)propyl]piperazine hydrochloride (112 mg).

$[\alpha]_D^{23}$: -16.3° (C=0.50, MeOH)

IR (Neat) : 3450, 2800, 2620, 1660, 1430, 1280, 1185, 1140 cm^{-1}

NMR (DMSO-d_6, δ) : 1.94-5.16 (29H, m), 6.62-8.35 (7H, m)

MASS : 615 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{37}ClF_6N_4O_3 \cdot 1.36H_2O$:
C 53.34, H 5.93, N 8.29

Found : C 53.33, H 5.79, N 8.06

Example 27

To a mixture of (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)piperazine (3.71 g) and 4-formyl-1-(triphenylmethyl)pyrazole (3.66 g) in 1,2-dichloroethane (80 ml) was added sodium triacetoxyborohydride (2.86 g). After stirring at room temperature for 3 hours, aqueous sodium bicarbonate solution was added to the mixture and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was dissolved in dichloromethane (40 ml) and added to a mixture of trifluoroacetic acid (30 ml) and anisole (15 ml).

After stirring for 7.5 hours at room temperature, the mixture was quenched with 10% sodium hydroxide (150 ml) and aqueous sodium bicarbonate and extracted with dichloromethane. The extract was washed with aqueous sodium bicarbonate solution and brine successively, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane (3:7) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(4-pyrazolylmethyl)piperazine (2.84 g).

NMR (DMSO-d_6, δ) : 2.04-2.14 (6H, m), 2.60-4.76 (11H, m), 6.49-6.54 (1H, m), 6.86-6.96 (2H, m), 7.45 (2H, br s), 7.64-7.68 (2H, m), 8.14 (1H, m)

MASS : 525 $(M+H)^+$

Example 28

Potassium carbonate (158 mg) and 2-bromoethanol (0.045 ml) were added to a solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(4-pyrazolylmethyl)piperazine (300 mg) in N,N-dimethylformamide (3 ml) at room temperature with stirring. After stirring at 100°C for 5 hours, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure. The obtained residue was purified by column chromatography (30 ml) on silica gel using a mixture of ethyl acetate and hexane (3:7) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]methyl]piperazine (255.2 mg).

IR (KBr) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 2.04-2.15 (6H, m), 2.60-4.80 (11H, m), 3.67-3.75 (2H, m), 4.10 (2H, t, J=5.7Hz), 4.86 (1H, t, J=5.3Hz), 6.50-6.56 (1H, m), 6.90-6.98 (2H, m), 7.36 (1H, br s), 7.43 (1H, br s), 7.61 (1H, br

s), 7.67 (1H, br s), 8.13 (1H, br s)

MASS : 569 $(M+H)^+$

Example 29

To a solution of (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)-4-[[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]methyl]piperazine (152 mg) in ethyl acetate (2 ml) was added triethylamine (0.048 ml) and methanesulfonyl chloride (0.027 ml) at room temperature. After stirring for 10 minutes, the mixture was quenched with water and extracted with ethyl acetate. The combined extracts were washed with water and brine successively, dried over magnesium sulfate, and evaporated under reduced pressure. The obtained residue was dissolved with N,N-dimethylformamide (2 ml) and added morpholine (0.028 ml), potassium carbonate (74 mg) and potassium iodide (13 mg). After stirring at 70°C for 6 hours, the mixture was quenched with water and extracted with ethyl acetate. The combined extracts were washed with water and brine successively, dried over magnesium sulfate, and evaporated under reduced pressure. The obtained residue was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate (0.2 ml) at room temperature. The mixture was added hexane, filtered, and dried over reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)-4-[[1-(2-morpholinoethyl)-1H-pyrazol-4-yl]methyl]piperazine dihydrochloride (188.7 mg) as a solid.

mp : 115-116°C

$[\alpha]_D^{25}$: -9.70° (C=0.50, MeOH)

IR (KBr) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 2.06-2.16 (6H, m), 2.85-5.00 (23H, m), 6.60-6.64 (1H, m), 6.91-7.08 (2H, m), 7.57 (1H, s), 7.74 (1H, br s), 7.78 (1H, br s), 8.10 (1H, br s), 8.18 (1H, br s)

MASS : 638 $(M+H)^+$ (free)

Example 30

A solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(4-chloro-2-butynyl)-2-(2-naphthylmethyl)piperazine (200 mg), 3-(aminomethyl)pyridine (47 mg), and triethylamine (0.08 ml) in acetonitrile (2 ml) was stirred under reflux for 3 hours and evaporated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (10 ml) using dichloromethane-methanol (30:1) as eluent. The obtained oil was dissolved in ethyl acetate and treated with a solution of 4N hydrogen chloride in ethyl acetate. The mixture was evaporated under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(3-pyridylmethylamino)-2-butynyl]-2-(2-naphthylmethyl)piperazine trihydrochloride (60 mg) as a powder.

$[\alpha]_D^{29}$: -20.80° (C=0.25, MeOH)

IR (Neat) : 3650-3100, 2750-1950, 1630, 1273, 1122 cm^{-1}

NMR (DMSO-d_6, δ): 2.60-5.30 (16H, m), 7.00-9.10 (14H, m)

MASS : 625 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{34}H_{33}Cl_3F_6N_4O \cdot 3.3H_2O$:
C 51.43, H 5.03, N 7.06

Found : C 51.42, H 4.91, N 6.78

Example 31

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(4-chloro-2-butynyl)-2-(2-naphthylmethyl)piperazine (300 mg), cis-2,6-dimethylmorpholine (94 mg) and powdered potassium carbonate (210 mg) in dry N,N-dimethylformamide (5 ml) was stirred at room temperature overnight. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the obtained residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane (4:1) as eluent. The obtained product was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-

[4-(cis-2,6-dimethylmorpholino)-2-butynyl]-2-(2-naphthylmethyl)piperazine dihydrochloride (170 mg).

IR (KBr) : 3428, 2931, 2559, 1644, 1432, 1282, 1184 cm^{-1}

NMR (DMSO-d_6, δ) : 1.13 (3H, s), 1.16 (3H, s), 2.60-5.40 (21H, m), 7.00-8.15 (10H, m)

MASS : 632 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{34}H_{37}Cl_2F_6N_3O_2 \cdot 2H_2O$: C 55.14, H 5.58, N 5.67

Found : C 54.89, H 5.59, N 5.31

Example 32

The following compound was obtained according to a similar manner to that of Example 31.

1,3-[Bis(trifluoromethyl)benzoyl]-4-[4-(2-methylthiazol-4-yl)methyl]-2-[(1H-indol-3-yl)methyl]piperazine hydrochloride

NMR (DMSO-d_6, δ) : 2.65 (3H, s), 3.00-5.20 (11H, m), 6.80-8.24 (9H, m), 10.93 (1H, br d)

MASS : 567 $(M+H)^+$ (free)

Example 33

To a stirred mixture of (2R)-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)piperazine (943 mg) and potassium carbonate (880 mg) in dimethylformamide (10 ml) was added propargyl bromide (0.2 ml) at room temperature. After 1 hour, the reaction mixture was poured into water (100 ml) and extracted with ethyl acetate. The extract was washed with brine and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate (5:1) as eluent to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-propargylpiperazine (1.09 g) as an oil.

NMR (DMSO-d_6, δ) : 2.00-2.20 (6H, m), 2.20-5.00 (12H,

m), 6.60-8.20 (6H, m)

MASS : 483 $(M+H)^+$

Example 34

A mixture of (2R)-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-propargylpiperazine (286 mg), (3S)-3-isopropylmorpholine hydrochloride (118 mg) and N,N-diisopropylamine (92 mg) in dioxane (3 ml) was stirred at room temperature. Paraformaldehyde (22 mg) and copper(I) chloride (10 mg) were added and the whole was stirred for 30 minutes and then heated at 80°C for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate (1:1) as eluent. The obtained product was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-((3S)-3-isopropylmorpholino)-2-butynyl]-2-(3,4-dimethylbenzyl)piperazine dihydrochloride (190 mg).

IR (KBr) : 3438, 2971, 2551, 1644, 1438, 1282, 1216, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 1.01 (6H, d, J=6.8Hz), 2.09-2.17 (6H, m), 2.36 (1H, m), 2.60-5.30 (22H, m), 6.60-8.30 (6H, m)

MASS : 624 $(M+H)^+$ (free)

Example 35

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(4-chloro-2-butenyl)-2-(3,4-dimethylbenzyl)piperazine (150 mg), (3S)-3-isopropylmorpholine hydrochloride (47 mg) and powdered potassium carbonate (117 mg) in dry N,N-dimethylformamide (1 ml) was stirred at 50°C for 1.5 hours. The reaction mixture was poured into water (10 ml) and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After evaporation of

the solvent, the obtained residue was purified by column chromatography on silica gel using ethyl acetate as eluent. The obtained product was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-((3S)-3-isopropylmorpholino)-2-butenyl]-2-(3,4-dimethylbenzyl)-piperazine dihydrochloride (110 mg).

IR (KBr) : 3430, 2971, 2661, 1644, 1434, 1280, 1135, 985, 680 cm^{-1}

NMR (DMSO-d_6, δ) : 1.01 (6H, m), 2.00-2.20 (6H, m), 2.40 (1H, m), 2.60-5.20 (24H, m), 6.60-8.20 (6H, m)

MASS : 626 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{33}H_{43}Cl_2F_6N_3O_2 \cdot 3H_2O$:
C 52.66, H 6.56, N 5.58
Found : C 52.45, H 6.55, N 5.49

Example 36

To a stirred solution of (2R)-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-((3R,3S)-3-hydroxy-methylpiperidino)ethyl]piperazine (133 mg) in N,N-dimethyl-formamide (1 ml) was added 60% sodium hydride (109 mg) at ice-salt bath temperature. A solution of ethyl iodide (53 mg) in N,N-dimethylformamide (0.5 ml) was added and the whole was stirred for 15 minutes and then at room temperature for 1 hour. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate. The extract was washed with brine and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel using a mixture of dichloromethane and methanol (10:1) as eluent. The obtained product was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-((3R,3S)-3-ethoxymethylpiperidino)-ethyl]piperazine dihydrochoride (101 mg).

$[\alpha]_D^{23}$: -8.0° (C=0.50, MeOH)

IR (KBr) : 3400, 2630, 2540, 1645, 1435, 1280, 1180, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 0.72-5.24 (32H, m), 1.12 (3H, t), 6.62-8.26 (6H, m)

MASS : 614 $(M+H)^+$ (free)

Example 37

The requisite mesylate was prepared by the treatment of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(2-hydroxyethyl)piperazine with methanesulfonyl chloride. A mixture of the mesylate (200 mg) and 4-hydroxymethylpiperidine hydrochloride (66 mg) in methanol (1 ml) was heated at reflux in the presence of potassium carbonate (150 mg). After 3 hours, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel using a mixture of dichloromethane and methanol (5:1) as eluent. The obtained product was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[2-(4-hydroxymethylpiperidino)ethyl]-2-(3,4-dimethylbenzyl)-piperazine dihydrochloride (32 mg).

$[\alpha]_D^{26}$: -5.8° (C=0.50, MeOH)

IR (KBr) : 3370, 2600, 1645, 1430, 1280, 1180, 1140 cm^{-1}

NMR (DMSO-d_6, δ) : 1.40-5.24 (30H, m), 6.60-8.24 (6H, m), 8.45 (1H, s)

MASS : 586 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{37}F_6N_3O_2 \cdot 2HCl \cdot 4.85H_2O$: C 48.36, H 6.57, N 5.64

Found : C 48.31, H 5.95, N 4.96

Example 38

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(4-chloro-2-butynyl)-2-(3,4-dimethylbenzyl)piperazine (150 mg), (3S)-3-ethylmorpholine hydrochloride (47 mg) and

powdered potassium carbonate (117 mg) in dry N,N-dimethylformamide (1 ml) was stirred at 50°C for 1.5 hours. The reaction mixture was poured into water (10 ml) and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the obtained residue was purified by column chromatography on silica gel using ethyl acetate as eluent. The obtained product was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-((3S)-3-ethylmorpholino)-2-butynyl]-2-(3,4-dimethylbenzyl)piperazine dihydrochloride (177 mg).

$[\alpha]_D^{26}$: 4.8° (C=0.50, MeOH)

IR (KBr) : 3430, 2580, 1645, 1435, 1280, 1180, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 1.27 (3H, t), 1.45-5.20 (28H, m), 6.64-8.28 (6H, m)

MASS : 610 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{32}H_{37}F_6N_3O_2 \cdot 2HCl \cdot 3.5H_2O$: C 51.55, H 6.22, N 5.64

Found : C 51.61, H 6.02, N 5.60

Example 39

The requisite mesylate was prepared by the treatment of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(2-hydroxyethyl)piperazine (150 mg) with methanesulfonyl chloride (37 mg). A mixture of the mesylate and (3S)-3-ethylmorpholine hydrochloride (51 mg) in N,N-dimethylformamide (1 ml) was heated at 50°C in the presence of potassium carbonate (85 mg). After 2 hours, the reaction mixture was poured into water (10 ml) and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the obtained residue was purified by column chromatography on silica gel using ethyl acetate as eluent. The obtained product was dissolved in ethyl acetate and treated with 4N

hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[2-((3S)-3-ethylmorpholino)ethyl]-2-(3,4-dimethylbenzyl)-piperazine dihydrochloride (45 mg).

$[\alpha]_D^{24}$: 1.60° (C=0.50, MeOH)

IR (KBr) : 3430, 2610, 1645, 1435, 1280, 1180, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 0.95 (3H, s), 1.16-5.20 (28H, m), 6.64-8.24 (6H, m)

MASS : 586 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{37}F_6N_3O_2 \cdot 2HCl \cdot 1.8H_2O$: C 52.15, H 6.21, N 6.08

Found : C 52.15, H 6.42, N 6.00

Example 40

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(2-methylsulfonyloxyethyl)-2-(2-naphthylmethyl)piperazine (200 mg), 3-(N-methylaminomethyl)pyridine dihydrochloride (73 mg) and triethylamine (120 mg) in dry methanol (5 ml) was refluxed for 4 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and methanol (10:1) as eluent to afford an oily product, which was treated with 4N hydrogen chloride in ethyl acetate (0.5 ml) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[2-[(N-methyl-N-(3-pyridylmethyl)amino]ethyl]-2-(2-naphthylmethyl)piperazine dihydrochloride (78 mg).

$[\alpha]_D^{25}$: -12.9° (C=0.50, MeOH)

IR (KBr) : 3410, 2600, 1640, 1430, 1280, 1180, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 2.40-5.28 (15H, m), 2.74 (3H, s), 7.00-9.10 (14H, m)

MASS : 615 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{33}H_{32}F_6N_4O \cdot 2HCl \cdot 4.6H_2O$:
C 51.45, H 5.65, N 7.27
Found : C 51.40, H 5.37, N 7.07

Example 41

The following compound was obtained according to a similar manner to that of Example 40.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[2-[N-methyl-N-(3-pyridylmethyl)amino]ethyl]-piperazine dihydrochloride

$[\alpha]_D^{24}$: -0.8° (C=0.50, MeOH)

IR (KBr) : 3400, 2600, 1640, 1280, 1180, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 1.12-5.20 (15H, m), 2.84 (3H, s), 6.63-9.00 (12H, m), 10,95 (1H, s)

MASS : 604 $(M+H)^+$

Elemental Analysis Calcd. for $C_{31}H_{31}F_6N_5O \cdot 2HCl \cdot 4.5H_2O$:
C 49.15, H 5.59, N 9.24
Found : C 49.19, H 5.41, N 9.08

Example 42

To a stirred mixture of (2R)-1-[3,5-[bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[N-(1-piperazinyl)carbamoylmethyl]piperazine dihydrochloride (500 mg) and triethylamine (302 mg) in tetrahydrofuran (10 ml) was added a solution of benzyl 4-bromobutanoate (192 mg) in tetrahydrofuran (2 ml) at room temperature for 24 hours. As a part of starting material remained, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. To the resulting residue were added benzyl 4-bromobutanoate (192 mg), potassium carbonate (310 mg) and N,N-dimethylformamide (2 ml). The whole was stirred at room temperature for 7 hours and then diluted with ethyl acetate and filtered. The filtrate was washed with brine and dried over magnesium sulfate. After evaporation of solvent, the

residue was purified by column chromatography on a silica gel using a mixture of ethyl acetate and methanol (5:1) as eluent to afford (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[N-[4-(3-benzyloxycarbonylpropyl)piperazin-1-yl]carbamoylmethyl]-2-[(1H-indol-3-yl)methyl]piperazine (296 mg).

IR (Neat) : 3250, 1720, 1670, 1630, 1430, 1350, 1270, 1120 cm^{-1}

NMR ($CDCl_3$, δ) : 1.60-3.66 (25H, m), 5.10 (2H, s), 6.80-7.86 (8H, m), 7.32 (5H, s), 8.21 (1H, s)

MASS : 773 $(M+H)^+$

Example 43

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[N-[4-(3-benzyloxycarbonylpropyl)piperazin-1-yl]-carbamoylmethyl]-2-[(1H-indol-3-yl)methyl]piperazine (1.3 g), ammonium formate (265 mg) and 10% palladium on activated carbon (130 mg) in water (2.5 ml) and ethanol (25 ml) was heated at 70°C with stirring under a nitrogen atmosphere. After 1 hour, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The product was triturated with ethyl ether to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[N-[4-(3-carboxypropyl)-piperazin-1-yl]carbamoylmethyl]-2-[(1H-indol-3-yl)methyl]-piperazine (1.19 g) as a powder.

$[\alpha]_D^{28}$: -18.60° (C=0.50, MeOH)

IR (Neat) : 3200, 1680, 1620, 1425, 1275, 1120 cm^{-1}

NMR ($CDCl_3$, δ) : 1.72-4.60 (25H, m), 6.71-7.93 (8H, m)

MASS : 683 $(M+H)^+$

Example 44

The following compounds were obtained according to a similar manner to that of Example 5-(1).

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[(2E)-3-[(3R)-4-(tert-butoxycarbonyl)morpholin-3-yl]-2-

propenyl]-2-(3,4-dimethylbenzyl)piperazine
IR (Neat) : 2973, 1697, 1645 cm^{-1}
NMR ($CDCl_3$, δ) : 1.39 (9H, s), 2.00-2.16 (6H, m), 2.48-5.00 (18H, m), 5.40-5.80 (2H, m), 6.60-6.80 (1H, m), 6.90-7.20 (2H, m), 7.30-7.70 (3H, m), 8.13 (1H, br s)
MASS : 670 $(M+H)^+$

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[(2E)-3-[(2R,2S)-4-(tert-butoxycarbonyl)morpholin-2-yl]-2-propenyl]-2-(3,4-dimethylbenzyl)piperazine
NMR (DMSO-d_6, δ) : 1.41 (9H, s), 2.08-2.16 (6H, m), 2.50-4.80 (18H, m), 5.55-5.85 (2H, m), 6.60-6.80 (1H, m), 6.90-7.20 (2H, m), 7.30-7.70 (2H, m), 8.13 (1H, br s)
MASS : 670 $(M+H)^+$

Example 45

A solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[(2E)-3-[(3R)-4-(tert-butoxycarbonyl)morpholin-3-yl]-2-propenyl]-2-(3,4-dimethylbenzyl)piperazine (1.36 g) in ethyl acetate (13 ml) was treated 4N hydrogen chloride in ethyl acetate (3.12 ml) at room temperature for 18 hours and then at 40°C for 5 hours. The solution was diluted with hexane and stirred for 1 hour. The resulting precipitate was collected by filtration and dried under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[(2E)-3-[(3R)-3-morpholinyl]-2-propenyl]-piperazine dihydrochloride (1.11 g) as a white powder.
mp : 225-232°C
$[\alpha]_D^{25}$: -12.00° (C=0.50, MeOH)
IR (KBr) : 1645 cm^{-1}
NMR (DMSO-d_6, δ) : 2.10-2.18 (6H, m), 2.70-5.10 (18H, m), 5.80-6.25 (2H, m), 6.60-6.70 (1H, m), 6.90-7.20 (2H, m), 7.39-7.69 (2H, m), 8.15-8.20 (1H, m),

9.60-10.0 (2H, m)

MASS : 570 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{29}H_{33}F_6N_3O_2 \cdot 2HCl \cdot 1.0H_2O$:
C 52.73, H 5.65, N 6.36

Found : C 52.65, H 5.76, N 6.26

Example 46

To a solution of (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)-4-(4-pyrazolylmethyl)-piperazine (500 mg) and tert-butyl bromoacetate (225 mg) in N,N-dimethylformamide (7.5 ml) was added potassium carbonate (390 mg), and the mixture was stirred at 60°C for 7 hours. Water was added to the mixture and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, evaporated under reduced pressure, and purified by column chromatography on a silica gel using a mixture of ethyl acetate and hexane (1:1) as eluent to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-(tert-butoxycarbonylmethyl)-1H-pyrazol-4-yl]methyl]-2-(3,4-dimethylbenzyl)piperazine as an oil.

NMR (DMSO-d_6, δ) : 1.01 (9H, s), 2.05-2.15 (6H, s), 2.52-4.90 (11H, m), 4.90 (2H, s), 6.53-6.58 (1H, m), 6.90-7.00 (2H, m), 7.41 (2H, s), 7.65 (2H, s), 8.13 (1H, br s)

MASS : 639 $(M+H)^+$

Example 47

A solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-(tert-butoxycarbonylmethyl)-1H-pyrazol-4-yl]methyl]-2-(3,4-dimethylbenzyl)piperazine (425 mg) in dichloromethane (2.5 ml) was treated with trifluoroacetic acid (2.5 ml) at room temperature for 1 hour. The mixture was adjusted to pH 7.4 with aqueous sodium bicarbonate solution and evaporated under reduced pressure. The residue was washed with a mixture of dichloromethane and methanol (9:1), and the

solution was evaporated under reduced pressure and purified by column chromatography on a silica gel using a mixture of methanol and chloroform (1:9) as eluent and subsequent crystallization from ethyl acetate, isopropyl ether, and hexane to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[[1-(carboxymethyl)-1H-pyrazol-4-yl]methyl]-2-(3,4-dimethylbenzyl)piperazine (395 mg) as a white powder.

mp : 223-230°C

$[\alpha]_D^{25}$: -15.10° (C=0.50, MeOH)

IR (KBr) : 1683, 1604 cm^{-1}

NMR (DMSO-d_6, δ) : 2.06-2.15 (6H, m), 2.52-4.90 (11H, m), 4.54 (2H, s), 6.50-6.60 (1H, m), 6.90-7.00 (2H, m), 7.31 (1H, s), 7.40 (1H, s), 7.57-7.64 (2H, m), 8.14 (1H, s)

Example 48

To a solution of (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-4-[[1-(carboxymethyl)-1H-pyrazol-4-yl]methyl]-2-(3,4-dimethylbenzyl)piperazine (120 mg) in tetrahydrofuran (1 ml) were added 1-hydroxybenzotriazole hydrate (176 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (240 mg) and morpholine (0.11 ml) at room temperature, and the mixture was stirred at room temperature overnight. The mixture was quenched with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on a silica gel using a mixture of methanol and ethyl acetate (1:9) as eluent to give a crude oil (76.7 mg). The oil was dissolved in ethyl acetate (0.7 ml) and added 4N hydrogen chloride in ethyl acetate (0.15 ml) at room temperature. After the addition of isopropyl ether, the resulting precipitate was filtered off and dried under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[[1-(morpholinocarboxymethyl)-1H-pyrazol-4-

yl]methyl]piperazine hydrochloride (40 mg) as a powder.

mp : 120-130°C

$[\alpha]_D^{25}$: -19.40° (C=0.25, MeOH)

IR (KBr) : 1649 cm^{-1}

NMR (DMSO-d_6, δ) : 2.06-2.16 (6H, s), 2.52-5.00 (19H, m), 5.19 (2H, s), 6.55-6.62 (1H, m), 6.92-7.03 (2H, m), 7.44 (1H, s), 7.66-7.68 (2H, m), 7.92 (1H, br s), 8.19 (1H, br s)

MASS : 652 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{22}H_{35}F_6N_5O_3 \cdot HCl \cdot 2.6H_2O$:
C 52.30, H 5.65, N 9.53
Found : C 52.58, H 5.63, N 9.22

Example 49

The following compound was obtained according to a similar manner to that of Example 34.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[4-[(3S)-3-(2-methylpropyl)morpholino]-2-butynyl]piperazine dihydrochloride

mp : 125-138°C

$[\alpha]_D^{25}$: +13.90° (C=0.50, MeOH)

IR (KBr) : 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 0.80-1.80 (9H, m), 2.09-2.18 (6H, m), 2.83-5.13 (20H, m), 6.60-6.70 (1H, m), 6.96-7.14 (2H, m), 7.46 (1H, br s), 7.67 (1H, br s), 8.16 (1H, br s)

MASS : 638 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{34}H_{43}Cl_2F_6N_3O_2 \cdot 1.1H_2O$:
C 55.91, H 6.24, N 5.75
Found : C 56.24, H 6.75, N 5.74

Example 50

The following compound was obtained according to a similar manner to that of Example 31.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[4-[3-(spirocyclopropyl)morpholino]-2-butynyl]piperazine dihydrochloride

$[\alpha]_D^{27.9}$: -9.70° (C=0.50, MeOH)

IR (KBr) : 3700-3000, 2700-2200, 1645, 1534, 1463, 1280, 1184 cm^{-1}

NMR (DMSO-d_6, δ) : 0.90-1.00 (4H, m), 3.00-4.70 (19H, m), 6.60-8.20 (6H, m)

MASS : 608 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{32}H_{35}F_6N_3O_2 \cdot 2HCl \cdot 2H_2O$: C 53.64, H 5.77, N 5.86

Found : C 53.92, H 6.05, N 5.61

Example 51

The following compounds were obtained according to a similar manner to that of Example 1-(1).

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(4-methoxypyridin-3-yl)-2-propynyl]-piperazine

NMR ($CDCl_3$, δ) : 2.00-5.20 (11H, m), 3.92 (3H, s), 6.80-8.00 (11H, m), 8.30 (1H, br s)

MASS : 601 $(M+H)^+$ (free)

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(4-methoxypyridin-3-yl)-2-propynyl]piperazine

NMR ($CDCl_3$, δ) : 2.00-5.20 (17H, m), 3.93 (3H, s), 6.60-8.80 (9H, m), 8.02 (1H, s), 8.30-8.50 (1H, m)

MASS : 590 $(M+H)^+$

Example 52

The following compounds were obtained according to a similar manner to that of Example 5-(2).

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(4-methoxypyridin-3-yl)-2-propynyl]-piperazine dihydrochloride

mp : 162-167°C

$[\alpha]_D^{26.6}$: +4.90° (C=0.50, MeOH)

IR (KBr) : 3700-3300, 2700-2300, 1641, 1502, 1430, 1363, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 3.00-5.20 (14H, m), 6.60-8.30 (9H, m), 8.80-9.90 (2H, m), 10.96 (1H, br s)

MASS : 601 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{26}F_6N_4O_2 \cdot 2HCl \cdot 2.2H_2O$:
C 52.16, H 4.91, N 8.32
Found : C 52.21, H 4.58, N 7.86

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(4-methoxypyridin-3-yl)-2-propynyl]piperazine dihydrochloride

mp : 150-153°C

$[\alpha]_D^{24.9}$: -7.45° (C=0.55, MeOH)

IR (KBr) : 3600-3300, 2700-2200, 1639, 1500, 1430, 1317, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-2.20 (6H, m), 2.80-5.20 (11H, m), 6.60-7.80 (6H, m), 8.20 (1H, br s), 8.81-8.97 (2H, m)

MASS : 590 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{29}F_6N_3O_2 \cdot 2HCl \cdot 2.2H_2O$:
C 52.97, H 5.27, N 5.93
Found : C 53.03, H 5.08, N 5.98

Example 53

The following compounds were obtained according to a similar manner to that of Example 3.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(4-methoxypyridin-3-yl)propyl]piperazine

dihydrochloride

mp : 165-170°C

$[\alpha]_D^{24.9}$: -1.91° (C=0.55, MeOH)

IR (KBr) : 3700-2300, 1643, 1502, 1432, 1363, 1280, 1222 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-2.30 (2H, m), 2.60-5.20 (16H, m), 6.60-8.30 (9H, m), 8.70-8.90 (2H, m), 10.95 (1H, br s), 11.60-11.80 (2H, m)

MASS : 605 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{30}F_6N_4O_2 \cdot 2HCl \cdot 2.8H_2O$: C 51.15, H 5.21, N 7.70

Found : C 51.11, H 5.40, N 7.61

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(4-methoxypyridin-3-yl)propyl]-piperazine dihydrochloride

mp : 159-168°C

$[\alpha]_D^{26.9}$: -10.91° (C=0.55, MeOH)

IR (KBr) : 3600-3300, 2700-2300, 1643, 1502, 1430, 1361, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-5.20 (21H, m), 4.13 (3H, s), 6.60-7.80 (6H, m), 8.20-8.30 (1H, m), 8.70-8.90 (2H, m), 11.60-11.90 (2H, m)

MASS : 594 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{33}F_6N_3O_2 \cdot 2HCl \cdot 2.4H_2O$: C 52.50, H 5.97, N 5.60

Found : C 52.46, H 5.65, N 5.92

Example 54

A solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-[6-(tert-butoxycarbonylamino)-pyridin-3-yl]-2-propynyl]piperazine (127 mg) prepared by a similar manner to that of Example 5-(1) and trifluoroacetic acid (5 ml) in dichloromethane (5 ml) was stirred at room temperature for 2 hours. The reaction mixture was

concentrated under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate and concentrated under reduced pressure. The syrup obtained was dissolved into ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)-methyl]-4-[3-(6-aminopyridin-3-yl)-2-propynyl]piperazine dihydrochloride (80 mg).

mp : 190-195°C

$[\alpha]_D^{24.0}$: -13.47° (C=0.23, MeOH)

IR (KBr) : 3600-3000, 2700-2500, 1668, 1619, 1428, 1359, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 3.00-5.20 (11H, m), 6.60-7.50 (6H, m), 7.70-8.30 (5H, m), 8.20-8.50 (2H, m), 11.95-11.10 (1H, br s)

MASS : 586 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{25}F_6N_5O \cdot 2HCl \cdot 2.5H_2O$:
C 51.22, H 4.58, N 9.95

Found : C 51.17, H 4.40, N 9.27

Example 55

The following compound was obtained according to a similar manner to that of Example 54.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(6-aminopyridin-3-yl)-2-propynyl]-piperazine dihydrochloride

mp : 183-189°C

IR (KBr) : 3600-2500, 1644, 1596, 1525, 1375, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-2.25 (6H, m), 2.80-5.25 (13H, m), 6.60-8.40 (9H, m), 8.00-8.80 (2H, m)

MASS : 575 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{28}F_6N_4O \cdot 2HCl \cdot 1.5H_2O$:
C 53.42, H 4.93, N 8.31

Found : C 53.08, H 5.01, N 8.12

Example 56

The following compounds were obtained according to a similar manner to that of Example 5.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)-4-[3-(2-pyridyl)-2-propynyl]piperazine
IR (KBr) : 3700-3200, 1641, 1278, 1136 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-4.00 (9H, m), 4.30-5.20 (2H, m), 7.00-8.65 (14H, m)
MASS : 582 $(M+H)^+$, 467

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[(2E)-3-(3-pyridyl)-2-propenyl]piperazine dihydrochloride
mp : 195-203°C
$[\alpha]_D^{24.9}$: -11.20° (C=0.50, MeOH)
IR (KBr) : 3600-3300, 2700-2500, 1644, 1430, 1363, 1280, 1184 cm^{-1}
NMR (DMSO-d_6, δ) : 3.00-5.20 (11H, m), 6.60-7.60 (6H, m), 7.70-9.00 (8H, m), 11.00 (1H, br s), 12.00-12.40 (2H, m)
MASS : 573 $(M+H)^+$ (free)
Elemental Analysis Calcd. for $C_{30}H_{26}F_6N_4O \cdot 2HCl \cdot 2.5H_2O$: C 52.18, H 4.82, N 8.11
Found : C 51.94, H 4.77, N 7.77

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[(2Z)-3-(3-pyridyl)-2-propenyl]-piperazine dihydrochloride
mp : 170-174°C
$[\alpha]_D^{23.0}$: -7.30° (C=0.50, MeOH)
IR (KBr) : 3600-3300, 2700-2500, 1644, 1550, 1430, 1363, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 2.00-2.30 (6H, m), 2.80-5.20 (11H, m), 6.40-8.40 (10H, m), 8.70-8.85 (2H, m), 12.00-12.20 (2H, m)

MASS : 562 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{29}F_6N_3O \cdot 2HCl \cdot 2.5H_2O$:
C 53.03, H 5.34, N 6.18
Found : C 52.99, H 5.41, N 5.91

(4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[4-(2-pyridyl)-3-butynyl]piperazine

NMR ($CDCl_3$, δ) : 1.80-5.20 (13H, m), 6.80-8.00 (12H, m), 8.19 (1H, s), 8.55 (1H, d, J=4.0Hz)

MASS : 585 $(M+H)^+$

Example 57

The following compounds were obtained according to a similar manner to that of Example 5.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(6-methoxypyridin-3-yl)propyl]-piperazine dihydrochloride

mp : 127-137°C

$[\alpha]_D^{22.5}$: -15.93° (C=0.16, MeOH)

IR (KBr) : 3600-3300, 2700-2500, 1646, 1556, 1434, 1280, 1184 cm^{-1}

NMR (DMSO-d_6, δ) : 1.90-5.20 (21H, m), 3.84 (3H, s), 6.60-7.30 (4H, m), 7.40-7.80 (3H, m), 8.00-8.30 (2H, m)

MASS : 594 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{33}F_6N_3O_2 \cdot 2HCl \cdot 1.2H_2O$:
C 54.11, H 5.48, N 6.11
Found : C 54.09, H 5.75, N 5.83

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[3-(6-methoxypyridin-3-yl)propyl]piperazine

dihydrochloride

mp : 195-200°C

$[\alpha]_D^{22.6}$: -2.03° (C=0.32, MeOH)

IR (KBr) : 3600-3300, 2700-2300, 1644, 1556, 1494, 1432, 1363, 1280, 1180 cm^{-1}

NMR (DMSO-d_6, δ) : 2.20-5.20 (15H, m), 3.79 (3H, s), 6.60-8.30 (11H, m), 10.95 (1H, br s), 11.60-11.80 (2H, m)

MASS : 605 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{30}F_6N_4O_2 \cdot 2HCl \cdot 1.5H_2O$: C 52.58, H 5.01, N 7.95

Found : C 52.89, H 5.40, N 7.63

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)-4-[3-(2-pyridyl)propyl]piperazine dihydrochloride

$[\alpha]_D^{26.8}$: -27.60° (C=0.50, MeOH)

IR (KBr) : 3700-3000, 2700-2200, 1647, 1279, 1136 cm^{-1}

NMR (DMSO-d_6, δ) : 2.20-4.30 (13H, m), 4.40-5.40 (2H, m), 7.00-8.90 (14H, m)

MASS : 586 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{32}H_{29}F_6N_3O \cdot 2HCl \cdot 2.5H_2O$: C 54.63, H 5.16, N 5.97

Found : C 54.55, H 5.37, N 5.56

(4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[4-(2-pyridyl)butyl]piperazine dihydrochloride

mp : 155-160°C

$[\alpha]_D^{27.0}$: +9.50° (C=0.10, MeOH)

IR (KBr) : 3700-3000, 2700-2200, 1641, 1459, 1428, 1280, 1137 cm^{-1}

NMR (DMSO-d_6, δ) : 1.70-2.20 (4H, m), 2.60-5.20 (13H, m), 6.60-8.80 (12H, m), 11.00 (1H, br s), 11.40-11.80 (2H, m)

MASS : 589 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{31}H_{30}F_6N_4O \cdot 2HCl \cdot 2.0H_2O$:
C 53.38, H 5.20, N 8.03

Found : C 53.34, H 5.38, N 7.78

Example 58

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]piperazine (0.83 g), methyl α-bromophenylacetate (0.42 g), potassium carbonate (1.0 g) in N,N-dimethylformamide (5 ml) was stirred at 50°C for 3 hours. The reaction mixture was poured into water and the resulting precipitates were collected by filtration. The precipitates were purified by column chromatography on silica gel using a mixture of dichloromethane and ethyl acetate as eluent to give a mixture of diastereoisomers, methyl (2R,2S)-2-[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]piperazin-4-yl]-2-phenylacetate (1.00 g).

NMR ($CDCl_3$, δ) : 2.00-5.20 (4H, m), 3.69 (3H, s), 6.70-8.20 (14H, m)

MASS : 604 $(M+H)^+$ (free)

Example 59

A solution of the mixture of diastereoisomers, methyl (2R,2S)-2-[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]piperazin-4-yl]-2-phenylacetate (360 mg) and 1N sodium hydroxide (1.5 ml) in methanol (5 ml) was stirred at 50°C for 2 hours. The mixture was concentrated under reduced pressure until aqueous solution. The solution was diluted with water and the solution was made acidic (about pH 5) with diluted hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a mixture of diastereoisomers, (2R,2S)-2-[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-piperazin-4-yl]-2-phenylacetic acid (0.33 g).

NMR ($CDCl_3$, δ) : 2.20-5.80 (10H, m), 6.60-8.20 (14H, m)
MASS : 590 $(M+H)^+$ (free)

Example 60

Isobutyl chloroformate (0.116 ml) was added dropwise to a suspension of the mixture of diastereoisomers, (2R,2S)-2-[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)-methyl]piperazin-4-yl]-2-phenylacetic acid (0.5 g) and N-methylmorpholine (0.103 ml) in 1,2-dimethoxyethane (3 ml) under -18°C. After being stirred at the same temperature for 30 minutes, a solution of sodium borohydride (32 mg) in water (0.5 ml) was added to the mixture all at once. After being stirred at room temperature for 30 minutes, 1N sodium hydroxide solution was added to the mixture and the whole was stirred at room temperature for 1 hour. The mixture was neutralized with diluted hydrochloric acid, and extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed eluent of dichloromethane and methanol. The fractions containing the objective compound were collected and evaporated under reduced pressure to give a mixture of diastereoisomers, (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[(1R,1S)-1-phenyl-2-hydroxyethyl]-piperazine (0.42 g).

NMR ($CDCl_3$, δ) : 1.90-5.20 (13H, m), 6.60-8.20 (14H, m)
MASS : 576 $(M+H)^+$

Example 61

Methanesulfonyl chloride (0.058 ml) was added to a solution of the mixture of diastereoisomers, (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[(1R,1S)-1-phenyl-2-hydroxyethyl]piperazine (0.36 g) and triethylamine (0.16 ml) in dichloromethane (10 ml) under -18°C. After being stirred at the same temperature for 30

minutes, additional methanesulfonyl chloride (0.058 ml) and triethylamine (0.16 ml) were added to the mixture. After being stirred at the same temperature for further 30 minutes, the reaction mixture was washed with water, dried over magnesium sulfate and evaporated under reduced pressure to give the corresponding mesylate. A mixture of the mesylate and morpholine (0.4 ml) in 1,4-dioxane was stirred at 50° for 3 hours. The reaction mixture was concentrated under reduced pressure to give a syrup, which was partitioned between water and ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give the crude mixture of diastereoisomers, which was purified by column chromatography on silica gel using a mixed eluent of dichloromethane and methanol. The faster eluting fractions were collected, evaporated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate to give a diastereoisomer of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[(1R or 1S)-1-phenyl-2-morpholinoethyl]-piperazine dihydrochloride.

mp : 203-207°C

$[\alpha]_D^{21.7}$: -6.0° (C=0.25, MeOH)

IR (KBr) : 3700-3300, 3100-2200, 1641, 1450, 1432, 1363, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 2.40-5.20 (20H, m), 6.60-8.30 (8H, m), 10.95 (1H, s)

MASS : 644 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{34}H_{34}F_6N_4O_2 \cdot 2HCl \cdot 2/3H_2O$: C 55.97, H 5.16, N 7.68

Found : C 55.98, H 5.48, N 7.26

The slower eluting fractions were collected, evaporated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate to give a diastereoisomer of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[(1S

or 1R)-1-phenyl-2-morpholinoethyl]piperazine dihydrochloride.

mp : 207-212°C

$[\alpha]_D^{21.7}$: -3.33° (C=0.24, MeOH)

IR (KBr) : 3700-3200, 3000-2300, 1643, 1450, 1432, 1280, 1182 cm^{-1}

NMR (DMSO-d_6, δ) : 2.40-5.20 (20H, m), 6.55-8.35 (8H, m), 10.95 (1H, s), 11.00-12.10 (2H, m)

MASS : 644 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{34}H_{34}F_6N_4O_2 \cdot 2HCl \cdot 0.5H_2O$: C 56.20, H 5.13, N 7.71

Found : C 56.15, H 5.52, N 7.32

Example 62

The following compound was obtained according to a similar manner to that of Example 45.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-[(2R,2S)-2-morpholinyl]-2-propenyl]-piperazine dihydrochloride

mp : 160-163°C

$[\alpha]_D^{25}$: -12.50° (C=0.50, MeOH)

IR (KBr) : 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 2.08-2.18 (6H, m), 2.55-5.10 (18H, m), 5.80-6.20 (2H, m), 6.60-6.70 (1H, m), 6.90-7.20 (2H, m), 7.47-7.70 (2H, m), 8.15-8.20 (1H, m)

MASS : 570 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{29}H_{35}F_6N_3O_2 \cdot 2HCl \cdot 1.0H_2O$: C 52.59, H 5.65, N 6.34

Found : C 52.85, H 5.97, N 6.16

Example 63

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)piperazine (500 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 µl) in tetrahydrofuran (2.5 ml) was cooled to -30°C with stirring under nitrogen

atmosphere. Acrolein (90%, 0.225 ml) was added to the mixture while maintaining the temperature at -20 ~ -40°C for a period of 10 minutes and then the resulting mixture was stirred at 0°C. After 6 hours, the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the resulting residue was chromatographed on a silica gel using a mixture of hexane and ethyl acetate as eluent to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(2-formylethyl)piperazine (332 mg) as an oil.

NMR (DMSO-d_6, δ) : 1.60-4.90 (19H, m), 6.55-6.75 (1H, m), 6.90-7.15 (2H, m), 7.30-7.75 (2H, m), 8.13 (1H, br s), 9.70 (1H, s)

MASS : 501 $(M+H)^+$

Example 64

To a stirred mixture of 4-amino-3,3-dimethylmorpholine dihydrochloride (122 mg) in dichloromethane (5 ml) was added triethylamine (61 mg) at ice bath temperature. A solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(2-formylethyl)piperazine (150 mg) in dichloromethane (2 ml) was added and the resulting mixture was stirred at room temperature. After 30 minutes, the reaction mixture was concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel using a mixture of hexane and ethyl acetate as eluent and the desired product was treated with 4N hydrogen chloride in ethyl acetate to give (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(3,3-dimethylmorpholino-imino)propyl]piperazine dihydrochloride (122 mg).

IR (KBr) : 3425, 2700, 2625, 1645, 1430, 1280, 1180, 1135 cm^{-1}

NMR (DMSO-d_6, δ) : 1.06-1.40 (6H, m), 2.00-2.40 (6H,

m), 2.60-5.80 (19H, m), 6.64-8.30 (6H, m), 10.00-12.18 (2H, m)

MASS : 613 $(M+H)^+$(free)

Elemental Analysis Calcd. for $C_{31}H_{38}F_6N_4O_2 \cdot 2HCl \cdot 2H_2O$: C 51.60, H 6.15, N 7.76

Found : C 51.82, H 6.49, N 7.29

Example 65

To a stirred mixture of 4-aminohomomorpholine dihydrochloride (100 mg) in dichloromethane (5 ml) was added triethylamine (107 mg) at ice bath temperature. A solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(2-formylethyl)piperazine (200 mg) in dichloromethane (2 ml) was added and the resulting mixture was stirred at room temperature. After 30 minutes, the reaction mixture was concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel using a mixture of hexane and ethyl acetate as eluent to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(homomorpholinoimino)propyl]piperazine (110 mg) and an intermediate. This compound was dissolved in methanol (5 ml) and sodium borohydride (17 mg) was added at ice bath temperature. After 2 hours, additional sodium borohydride (40 mg) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and then extracted with dichloromethane. The extract was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the resulting residue was purified by a silica gel column chromatography using a mixture of dichloromethane and methanol (50:1) as eluent to give the desired product, which was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to afford (2R)-1-[3,5-bis-(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(homomorpholinoamino)propyl]piperazine dihydrochloride (66

mg).

$[\alpha]_D^{27}$: -13.7° (C=0.50, MeOH)

IR (KBr) : 3450, 2700, 2620, 1645, 1430, 1280, 1185, 1135 cm^{-1}

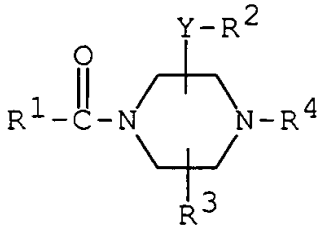
MASS : 601 $(M+H)^+$ (free)

Elemental Analysis Calcd. for $C_{30}H_{38}F_6N_4O_2 \cdot 2HCl \cdot 0.7H_2O$:
C 52.51, H 6.08, N 8.17

Found : C 52.51, H 6.05, N 7.86

What we claim is :

1. A compound of the formula :



wherein

Y is bond or lower alkylene,

R^1 is aryl which may have substituent(s),

R^2 is aryl or indolyl, each of which may have substituent(s),

R^3 is hydrogen or lower alkyl,

R^4 is pyridyl(lower)alkylamino(lower)alkynyl;
N-(lower alkyl)-N-[pyridyl(lower)alkyl]amino-(lower)alkyl;
hydroxy(lower)alkoxy(lower)alkyl;
lower alkanoyl(lower)alkoxy(lower)alkyl;
phenyl(lower)alkyl which may have lower alkoxycarbonyl, carboxy, hydroxy(lower)alkyl or morpholinyl(lower)alkyl;
(2-pyridyl)(lower)alkyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl and halogen;
(3-pyridyl)propyl which may have lower alkoxy;
(3-pyridyl)butyl;
(3-pyridyl)(lower)alkenyl;
(2-pyridyl)(lower)alkynyl;
(3-pyridyl)(lower)alkynyl which may have lower alkoxy or amino;
pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have substituent(s);

imidazolyl(lower)alkyl which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;
pyrazolyl(lower)alkyl which may have hydroxy(lower)alkyl, carboxy(lower)alkyl, lower alkoxycarbonyl(lower)alkyl, morpholinyl(lower)alkyl or morpholinylcarbonyl(lower)alkyl;
thiazolyl(lower)alkyl which may have lower alkyl; or
saturated heterocyclic(lower)alkyl,
saturated heterocyclic(lower)alkenyl,
saturated heterocyclic(lower)alkynyl,
saturated heterocyclicamino(lower)alkyl,
saturated heterocyclicimino(lower)alkyl,
saturated heterocyclicaminocarbonyl(lower)alkyl or
saturated heterocyclic(lower)alkoxy(lower)alkyl,
each of which may have substituent(s),
and a salt thereof.

2. The compound of claim 1, in which
Y is lower alkylene,
R^1 is C_6-C_{10} aryl which may have 1 or 2 mono(or di or tri)halo(lower)alkyl,
R^2 is C_6-C_{10} aryl or indolyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl and halogen,
R^3 is hydrogen, and
R^4 is pyridyl(lower)alkylamino(lower)alkynyl;
(2-pyridyl)propyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl and halogen;

pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl, ar(lower)alkyl and pyridyl(lower)alkyl;

imidazolyl(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

(2-methyl-1H-imidazol-4-yl)(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of isopropyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

(5-methyl-1H-imidazol-4-yl)(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of isopropyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

(3-morpholinyl)(lower)alkenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and aryl;

(3-morpholinyl)(lower)alkynyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and aryl;

morpholino(lower)alkynyl which have a subsitutuent selected from the group consisting of carbamoyl, lower alkylcarbamoyl, di(lower alkyl)carbamoyl, hydroxy(lower)alkyl and aryl;

[3-[mono(or di or tri)halo(lower)alkyl]morpholino]-(lower)alkynyl;

morpholino(lower)alkenyl which have aryl; or

morpholino(lower)alkynyl which have 1 or 2 subsitutuent(s) selected from the group consisting of lower alkyl, aryl and halogen at the 2nd

position of the morpholino group.

3. The compound of claim 2, in which
Y is lower alkylene,
R^1 is phenyl which have 2 trihalo(lower)alkyl,
R^2 is phenyl which have 2 lower alkyl,
R^3 is hydrogen, and
R^4 is (2-pyridyl)propyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl and halogen;
pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl, phenyl(lower)alkyl and pyridyl(lower)alkyl;
imidazolyl(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of lower alkynyl, phenyl(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;
(2-methyl-1H-imidazol-4-yl)(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of isopropyl, lower alkynyl, phenyl(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;
(5-methyl-1H-imidazol-4-yl)(lower)alkyl which have 1 or 2 substituent(s) selected from the group consisting of isopropyl, lower alkynyl, phenyl(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;
(3-morpholinyl)(lower)alkenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and phenyl;
(3-morpholinyl)(lower)alkynyl which may have 1 to 3 substituent(s) selected from the group consisting

of lower alkyl and phenyl;
morpholino(lower)alkynyl which have a subsitutuent selected from the group consisting of carbamoyl, lower alkylcarbamoyl, di(lower alkyl)carbamoyl, hydroxy(lower)alkyl and phenyl;
[3-[mono(or di or tri)halo(lower)alkyl]morpholino]-(lower)alkynyl;
morpholino(lower)alkenyl which have aryl; or
morpholino(lower)alkynyl which have 1 or 2 subsitutuent(s) selected from the group consisting of lower alkyl, phenyl and halogen at the 2nd position of the morpholino group.

4. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

5. A use of a compound of claim 1 as a medicament.

6. A method for treating or preventing Tachykinin-mediated diseases which comprises administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.

7. A compound of claim 1 for use as a medicament.

8. Use of a compound of claim 1 for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.